ARCHIVES OF SURGERY

VOLUME 34 APRIL 1937 NUMBER 4

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PERITONITIS

I. THE EFFECT ON BLOOD PRESSURE OF THE PERITONEAL CONTENT IN SUPPURATIVE AND IN BILE PERITONITIS

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One of the common hypotheses of the cause of death from peritonitis is that of vasomotor collapse incident to the absorption of toxins from the peritoneum. It has long been assumed that causative micro-organisms have been the source of the toxins, with the peritoneum acting merely as an absorptive membrane of a large surface area. As early as 1902 certain authors,[1] on the basis of experimental results, advocated preliminary nonspecific irritation of the peritoneum to prevent the absorption of toxins. They believed that peritoneal absorption was retarded by a fibrinous exudate. The physiology of the peritoneum is now better understood. This knowledge has been reviewed by Cunningham[2] and by Livingston.[3] Steinberg[4] clarified the situation with a clearcut series of experiments in which the diphtheria bacillus was used

Read in part before the Chicago Surgical Society, Feb. 7, 1936.

From the Douglas Smith Foundation and from the Service of Dr. Edmund Andrews, Department of Surgery, the University of Chicago.

1. Soleri, S.: Experimentelle Untersuchungen ueber die Veraenderungen des Widerstandes des Peritoneums gegen die Infection durch Bacterium Coli, Beitr. z. path. Anat. u. z. allg. Path. **31**:536, 1902. Miyake, H.: Experimentelle Studien zur Steigerung der Widerstandsfähigkeit der Gewebe gegen Infektion, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:719, 1904. Von Mikulicz, J.: Versuche ueber Resistenzvermehrung des Peritoneums gegen Infection bei Magen- und Daroperationen, Arch. f. klin. Chir. **73**:347, 1904. Von Graff, E.: Zur Behandlung von Laparotomien mit subkutaner Injektion von Nukleinsäure, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:466, 1912. Hoehne, O.: Ueber Toxinresorbtion aus der Bauchhöhle und ueber intraperitoneale Narkose, Zentralbl. f. Gynäk. **36**:258, 1912.

2. Cunningham, R. S.: Physiology of Serous Membranes, Physiol. Rev. **6**:271, 1926.

3. Livingston, E. M.: Clinical Study of the Abdominal Cavity and Peritoneum, New York, Paul B. Hoeber, Inc., 1932.

4. Steinberg, B.: The Cause of Death in Acute Diffuse Peritonitis, Arch. Surg. **23**:145 (July) 1931.

for intraperitoneal injection. While he found death to be due to the corresponding toxin, resistance was believed to be due to rapid phagocytosis, removing bacteria from the peritoneal cavity before the formation of a toxin could take place. This work, as well as the previous experiments of Gay and Morrison,[5] has been the point of departure for immunization of the peritoneum.[6]

That there is a toxic substance involved in death from intestinal obstruction has long been believed, as a result of the work of Murphy and Brooks,[7] Whipple, Stone and Bernheim,[8] Dragstedt and his co-workers[9] and others.[10] Recently, Scott and Wangensteen[11] showed that the peritoneal fluid removed from dogs dying of experimental intestinal strangulation was nontoxic unless an intestinal loop was actually gangrenous. Since paralytic ileus is frequently associated with

5. Gay, F. P., and Morrison, L. F.: Clasmatocytes and Resistance to Streptococcus Infection: V. Studies in Streptococcus Infection and Immunity, J. Infect. Dis. **33**:338, 1923.

6. Rankin, F. W., and Bargen, J. A.: Vaccination Against Peritonitis in Surgery of the Colon, Arch. Surg. **22**:98 (Jan.) 1931. Steinberg, B.: A Rapid Method of Protecting the Peritoneum Against Peritonitis, ibid. **24**:308 (Feb.) 1932. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, ibid. **18**: 2202 (April) 1929. Steinberg, B., and Goldblatt, H.: Protection of the Peritoneum Against Infection, Surg., Gynec. & Obst. **57**:15, 1933. Trenouth, A. M., and Bargen, J. A.: Peritoneal Reactions to Vaccine: Temperature Reactions After Intraperitoneal Vaccination, Proc. Staff Meet., Mayo Clin. **8**:583, 1933.

7. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Cause of Symptoms and Death, Arch. Int. Med. **15**:392 (March) 1915.

8. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, J. Exper. Med. **17**:286 and 307, 1913.

9. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **14**:17, 1916; Intestinal Obstruction: An Exerimental Study of the Intoxication in Closed Intestinal Loops, J. Exper. Med. **25**:421, 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, ibid. **30**:109, 1919.

10. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581 (Nov. 4) 1922; Chemical Studies on Intestinal Intoxication, J. Biol. Chem. **52**:111, 1922. Foster, W. C., and Hausler, R. W.: Acute Intestinal Obstruction: III. Simple Obstruction, Arch. Int. Med. **36**:31 (July) 1925. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16**:606 (Feb.) 1928. Wagensteen, O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, ibid. **16**:1089 (May) 1928.

11. Scott, H. G., and Wangensteen, O. H.: Effect of Intravenous Injections of Peritoneal Fluids Recovered from Dogs Dying from Experimental Intestinal Strangulations, Proc. Soc. Exper. Biol. & Med. **29**:559, 1932.

peritonitis, many authors [12] have thought that this same or a similar substance produced the toxemia of generalized peritonitis.

Although Steinberg and his co-workers [13] had previously reported a slight drop in blood pressure occurring during the development of suppurative peritonitis and Whipple [14] had barely mentioned a toxic proteose as being associated with peritonitis, we [15] were the first to demonstrate clearly the action of a vasodepressant toxic substance in peritonitis.

METHOD

It occurred to us that the vasomotor system of another animal might be more sensitive than that of the animal in which peritonitis was present. Normal dogs, weighing from 6 to 14 Kg., whose blood pressures were being observed by the direct method through a carotid cannula, were used as indicators of vasodepressant toxins. In the majority of experiments injections were made intravenously into dogs completely anesthetized with barbital (from 250 to 275 mg. per kilogram of body weight, intraperitoneally or intramuscularly). In some later experiments a few injections were made intraperitoneally into anesthetized dogs and intravenously into unanesthetized dogs. In the latter group, determinations of the blood pressure, when made, were obtained by direct puncture of the femoral artery. In about two thirds of the instances in which a drop in the blood pressure occurred, the same material was also tested by intravenous injection into a rabbit, since it has been shown by Dale and Laidlaw [16] that the vasomotor system of the rabbit responds to histamine with a rise in blood pressure. In every instance in our experiments that a preparation was found to be toxic in the dog, there was a similar action for the rabbit.

The method of Buchbinder, Heilman and Foster [17] of producing suppurative peritonitis by an open isolated intestinal segment, around which the continuity of the intestinal tract was reestablished by end to end or side to side anastomosis, has been used and found reliable. Only two dogs of the fifty so operated on survived. When leakage was present at the site of the anastomosis, the animals were discarded from the series, since Gatch, Trusler and Lyons [18] recently published

12. Orr, T. G., and Hayden, R. L.: Enterostomy in the Treatment of General Peritonitis, Arch. Surg. **18**:2159 (April) 1929. Benians, T. H. C.: Further Experiments with Fixation Areas, Bearing on the Pathogenicity of Bacillus Coli in Peritoneal Infections, Brit. J. Exper. Path. **5**:123, 1924. Bailey, H. A., and Shipley, A. M.: Treatment of Appendicitis Complicated by Peritonitis, Ann. Surg. **96**:537, 1932.

13. Steinberg, B.; Kobacker, J. L., and Russel, T. G.: Cardiovascular System in Acute Suppurative Peritonitis, Proc. Soc. Exper. Biol. & Med. **30**:1155, 1930.

14. Whipple, G. H.: Proteose Intoxication: Intestinal Obstruction, Peritonitis and Acute Pancreatitis, J. A. M. A. **67**:15 (July 1) 1916.

15. Harmon, P. H., and Harkins, H. N.: Depressor Substances in Peritonitis, Proc. Soc. Exper. Biol. & Med. **32**:6, 1934.

16. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**:355, 1919.

17. Buchbinder, J. R.; Heilman, F. R., and Foster, G. C.: Experimental Peritonitis: II. The Effect of Hypertonic Dextrose Solution upon Experimental Diffuse Peritonitis, Surg., Gynec. & Obst. **49**:788, 1929.

18. Gatch, W. D.; Trusler, H. M., and Lyons, R. E.: Toxemia in Acute Intestinal Obstruction, Arch. Surg. **28**:1102 (June) 1934.

results of experiments which showed the direct toxicity of intraperitoneally extravasated pancreaticoduodenal secretion.

Bile peritonitis was produced by three different methods: by the intraperitoneal injection of whole sterile gallbladder bile from dogs, by the intraperitoneal injection of 10 per cent solution of bile salts[19] sterilized either in the autoclave or by filtration through a sterile Berkefeld N filter, and by defundation of the gallbladder after double ligature and division of the common bile duct between ligatures.

Observations on the hemoglobin and the percentage by volume of red cells with a view of determining possible blood concentration were carried out on representative animals in each class of experiments. The Sahli hemoglobinometer (17 Gm. per hundred cubic centimeters equals 100 per cent) and the Van Allen hematocrit were used. The amount of blood obtainable from section of the carotid artery (bleeding volume) was determined on animals from each type of experiment. The latter observations will be presented, with the results of the corresponding experiment, later in the paper.

After a time varying from sixteen to ninety-six hours the peritoneal cavity was reopened under aseptic precautions, the contents were cultured and the peritoneal cavity was aspirated. In those animals in which suppurative peritonitis occurred it was usually necessary to lavage the peritoneum with from 150 to 300 cc. of physiologic solution of sodium chloride in order to obtain most of the purulent material. When bile peritonitis was produced, it was unnecessary to add fluid, since a large quantity of serosanguineous exudate mixed with bile salts or bile was present.[20] This exudate is rich in protein and corresponds closely in chemical composition to blood plasma.[21] The fluid obtained was then centrifugated at high speed for from thirty to forty-five minutes until either a clear or a slightly opalescent supernatant fluid remained. It was then removed carefully from the underlying sediment and from the overlying lipoid film and used in the experiments described here. Intravascular clotting was not observed in any experiments when such fluids were injected intravenously. These experiments were performed over a period of two years but are grouped together for ease in presentation without regard for chronological sequence.

EXPERIMENTAL DATA

EXPERIMENT 1 (table 1).—*Vasodepressant substances associated with peritonitis produced by an open low intestinal loop.*

Peritoneal washings were obtained from fifteen dogs in which suppurative peritonitis had been produced by an open intestinal loop, located within 20 cm. of the ileocecal junction. In many instances, as indicated in the table, opportunity was present for peritoneal lavage on separate days in the same animal. The result

19. Armour's purified bile salts were used.

20. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61, 1931. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of Bacillus Welchii Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, ibid. **53**:176, 1931. Mason, E. C., and Lemon, C. W.: Anhydremia as a Possible Cause of Death in Liver Autolysis, ibid. **55**:427, 1932. Trusler, H. M., and Reeves, J. R.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, Arch. Surg. **28**:479 (March) 1934.

21. Harkins, H. N.; Harmon, P. H.; Hudson, J., and Andrews, E.: Mechanism of Death in Bile Peritonitis, Proc. Soc. Exper. Biol. & Med. **32**:691, 1935. Harkins, H. N.; Harmon, P. H., and Hudson, J.: Lethal Factors in Bile Peritonitis: I. "Surgical Shock," Arch. Surg. **33**:576 (Oct.) 1936.

of a typical experiment is shown in chart 1. An open intestinal segment 27.5 cm. long was established on dog 215 (weight 9.5 Kg.). A side to side anastomosis was made at a point 3.5 cm. from the ileocecal junction. Seventy-five centimeters of intestine remained from the pylorus to the site of anastomosis. The peritoneal cavity was reopened twenty-four hours and again forty-eight hours after the first operation, aseptic lavage of the peritoneum with physiologic solution of sodium chloride being given on each occasion. A marked fall in blood pressure was obtained in tests of the supernatant fluid on other dogs. In the experiment reproduced in chart 1, 120 cc. of almost clear fluid from the centrifugated peritoneal washings was injected into the right femoral vein of dog 110 (weight 7 Kg.). The blood pressure was recorded by the direct method from the right carotid artery, the animal being under barbital anesthesia. The initial blood pressure was 126 mm. The injection required one and a half minutes. The blood pressure began

TABLE 1.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Suppurative Peritonitis Produced by an Open Intestinal Loop in the Lower Part of the Ileum*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
25	.....	.....	Present	.....	Heavy growth of Clostridia and B. coli
112	.....	.....	Present	.....	Same as in dog 25
215	Present	Present	.....	.....	Clostridia, B. coli, Str. viridans and Str. haemolyticus
337	Absent	.....	Present	.....	Same as in dog 215
338	Absent	.....	Present	Present	Same as in dog 215 with staphylococci
339	.....	Present	.....	.....	Clostridia, staphylococci and B. coli
442	.....	Present	.....	.....	Clostridia and B. coli
520	.....	Absent	.....	.....	Clostridia, staphylococci and B. coli
549	.....	Absent	.....	.....	B. coli, gram-positive aerobic bacilli and staphylococci
550	.....	Absent	.....	.....	B. coli and clostridia
617	.....	.....	Present	.....	B. coli, Clostridia and Str. haemolyticus
720	.....	.....	.....	Absent	B. coli, few staphylococci and streptococci (died in 9 days)
846	.....	.....	Absent	.....	Staph. albus and B. coli (mild and localized)
1438	.....	.....	Present	.....	B. coli and Str. haemolyticus
1443	.....	.....	.....	Present	B. coli, Str. haemolyticus, Staph. albus and an unidentified gram-positive bacillus

to fall as the injection was being terminated. Five minutes later the blood pressure was 28 mm. A slow rise then ensued, the level in the three steps in the tracing being 38, 70 and 90 mm.

From table 1 it is seen that a certain time is necessary for enough of the toxic substance to develop in the peritoneal cavity to be demonstrable under the conditions of these experiments. In only one of three dogs examined on the first day after the primary operation could the toxic substance be demonstrated, while in three of six examined forty-eight hours after the first operation and in six of seven examined after seventy-two hours the toxic substance was present.

EXPERIMENT 2 (table 2).—*Midintestinal loops.*

These experiments in which five dogs were used are similar to those described under experiment 1, except that the open loop was removed from the intestinal tract at approximately half the distance from the pylorus to the cecum.

While there were not as many animals in this group as in the preceding one, the data do not indicate any difference in the rate of production of the toxic substances in the two sets of experiments.

EXPERIMENT 3 (table 3).—*High intestinal loops.*

In this group eight dogs were used. Care was taken to select for the highest point of the open loop, a level at least 20 cm. below the pylorus, so that the entrance of the common bile duct and at least one of the pancreatic ducts was above the site of anastomosis. The mesenteric border of the open loop, which frequently contained a portion of the pancreas, was carefully examined for accessory pancreatic ducts. Whenever these were found they were divided between double ligatures of silk. These precautions were purposely not observed in the instances of dogs 547 and 548. In these animals especially high sites for the upper portion of the open loop were selected, i. e., 4 and 7 cm. from the pylorus, so that the open loop would contain the entrance of the common bile duct and at least one of the pancreatic ducts. These two dogs died in sixteen and twenty-two hours, respectively.

The peritoneal washings obtained before death from the latter two animals caused a profound drop in blood pressure and could be considered as confirmatory of the findings of Gatch, Trusler and Lyons[18] and of Dragstedt, Haymond and Ellis,[22] who reported that activated pancreatic juice within the peritoneum was toxic. Excluding these two special instances, there remains the fact that the

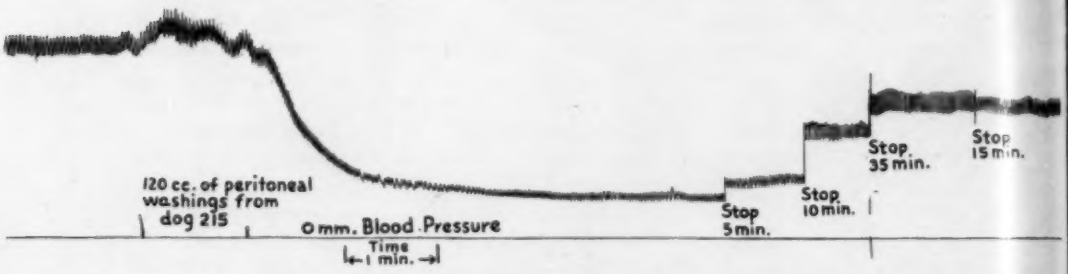

Chart 1.—Blood pressure tracing of a 7 Kg. dog given an intravenous injection of centrifugated peritoneal washings from a dog (no. 215) with suppurative peritonitis. Note the profound and almost immediate drop in arterial blood pressure and the slow return to an almost normal level.

washings from four of six animals were toxic within twenty-four hours after the intestinal loop was opened.

EXPERIMENT 4.—*The exudate in experimental bile peritonitis.*

Nine dogs were used in this division. Bile peritonitis was produced in three groups of three dogs each by the three methods previously indicated. Although the entire supernatant fluid from the centrifugated peritoneal washings of a single dog was injected intravenously into the test animal, no change in blood pressure was noted save the transient pressor effect due to an increase in circulating fluid volume immediately after injection. In a single instance, when the animal was not washed out until an hour after death, a typical profound drop in blood pressure occurred. In six of these instances a large gram-positive obligate anaerobic organism was obtained in pure culture. In two instances the cultures remained sterile,

22. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, Arch. Surg. **28**:232 (Feb.) 1934.

while from the last mentioned animal the gram-positive anaerobic bacillus was obtained in mixed culture with the colon bacillus.

EXPERIMENT 5.—*Control experiment; normal dogs.*

Lavage of the peritoneal cavity of eight normal animals was done. In four instances this procedure was repeated in forty-eight hours. Twelve samples of fluid from normal dogs were thus tested on other dogs. In not a single instance was a fall in blood pressure noted. Cultures for bacteria from these twelve fluids remained sterile.

EXPERIMENT 6.—*Second control experiment; washings after extensive gastro-intestinal operations.*

TABLE 2.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Peritonitis Produced by an Open Loop in the Region of of the Jejuno-Ileal Junction*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
214	Absent	.....	.....	.....	Staph. aureus, B. coli and few Clostridia
230	Absent	Present	.....	.....	Clostridia and B. coli
770	Present	.....	.....	.....	B. coli and few Clostridia
776	Absent	Present	.....	.....	B. coli and Clostridia (sterile on 1st day)
840	.....	Present	.....	.....	B. coli and Clostridia

TABLE 3.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Peritonitis Produced by an Open Loop in the Duodenum or in the Region of the Duodeno-Jejunal Junction*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
507	Slight fall	Present	.....	.....	Clostridia and B. coli
508	.....	Present	.....	.....	Same as in dog 507
547	Present	.....	.....	.....	Same as in dog 507
548	Present	.....	.....	.....	Same as in dog 507
771	Present	.....	.....	.....	Same as in dog 507
773	Present	.....	.....	.....	B. coli
775	Absent	.....	.....	.....	B. coli and Clostridia
790	Present	.....	.....	.....	B. coli, few Staph. albus and streptococci

In six instances a gastrojejunostomy without excision of any portion of the stomach was done after the method of Eiselsberg for pyloric exclusion, while on two other dogs a similar operation was done by the Billroth II technic. On the fourth postoperative day the peritoneum was reopened, cultures for bacteria were made and the peritoneal contents were removed by the usual method of lavage and aspiration. Table 4 shows the condition of the peritoneum and the results of the cultures for bacteria in these eight dogs. No vasodepressant substance was demonstrated.

EXPERIMENT 7.—*Filtration of toxic peritoneal washings.*

An open loop had been made in the lower level of the ileum of dog 617. On the third day after the primary operation the peritoneal cavity of this dog was reopened, and its content was removed by lavage and aspiration. Cultures of the content yielded Bacillus coli-communis, Streptococcus haemolyticus and a gram-positive

spore-forming obligate anaerobic organism. The clear supernatant fluid obtained by centrifugation was divided into two portions. One part was passed through a sterile Berkefeld N filter. The filtrate was cultured for bacteria, but no growth was obtained. Portions of both these fluids were then tested by intravenous injection into a normal anesthetized dog (chart 2), with the result that they caused a drop in blood pressure. The first two drops of 50 and 54 mm. were observed with the unfiltered samples, while the latter two drops in the blood pressure of 22 and 26 mm. were observed with the filtered samples. We have observed that succeeding identical doses of this toxic material frequently do not cause as profound a fall in the blood pressure as the initial dose, so that while this experiment possibly indicates some slight loss in potency by filtration, such a conclusion is not certain. The same phenomenon is seen after the intravenous injection of histamine. This experiment was repeated with an identical result with the fluid from dog 508.

EXPERIMENT 8.—*Does atropine abolish the vasodepressant action?*

It has been shown by Dale and Laidlaw [16] and by Simonart [23] that atropine will abolish the fall in the blood pressure that is produced by acetylcholine. Fluids

TABLE 4.—*Appearance of Peritoneum in Dogs Which Had an Extensive Gastro-Intestinal Operation Ninety-Six Hours Previously*

Dog No.	Type of Operation	Appearance of Peritoneum	Results of Culture for Bacteria
152	Eiselsberg	20 cc. of free fluid; not hyperemic	B. coli-communis and Staph. albus
153	Eiselsberg	Same as in dog 152	B. coli-communis
154	Eiselsberg	Same as in dog 152	Staph. aureus
244	Eiselsberg	40 cc. of purulent free fluid; moderately hyperemic	Str. haemolyticus, Str. viridans and Clostridia
261	Billroth II	20 cc. of free fluid; not hyperemic	Staph. aureus and an aerobic gram-positive bacillus
333	Billroth II	50 cc. of purulent free fluid; peritoneum markedly hyperemic	B. coli-communis and Clostridia
716	Eiselsberg	20 cc. of free fluid; not hyperemic	B. coli-communis, with slight growth of Str. haemolyticus and an aerobic gram-positive bacillus
818	Eiselsberg	20 cc. of free fluid; not hyperemic	Staph. aureus and Clostridia

from all eight animals used in this division had been previously shown to lower the blood pressure. Atropine sulfate, 0.8 mg., was then injected intravenously into the test animal in each case. The same dose of fluid that occasioned the first observed drop in the blood pressure was then readministered intravenously.

No single response was obtained in all dogs (charts 3 and 4). Atropine sulfate partially abolished the drop in blood pressure caused by the fluid from dog 339, while it had no effect on the reaction produced by the fluid from dog 338. Atropine sulfate rendered the test animals given the fluid from dogs 337 and 442 totally refractory to a second dose of the fluid. The fluid from dog 617 was similar to that from dog 339, as atropine sulfate partially abolished its depressant effect. Since there was an indication that a second dose of a vasodepressant fluid did not produce the same drop in blood pressure as the first, a few tests were made only after atropinization of the test animal. The results of such tests were com-

23. Simonart, A.: On the Action of Certain Derivatives of Choline, J. Pharmacol. & Exper. Therap. **46**:157, 1932.

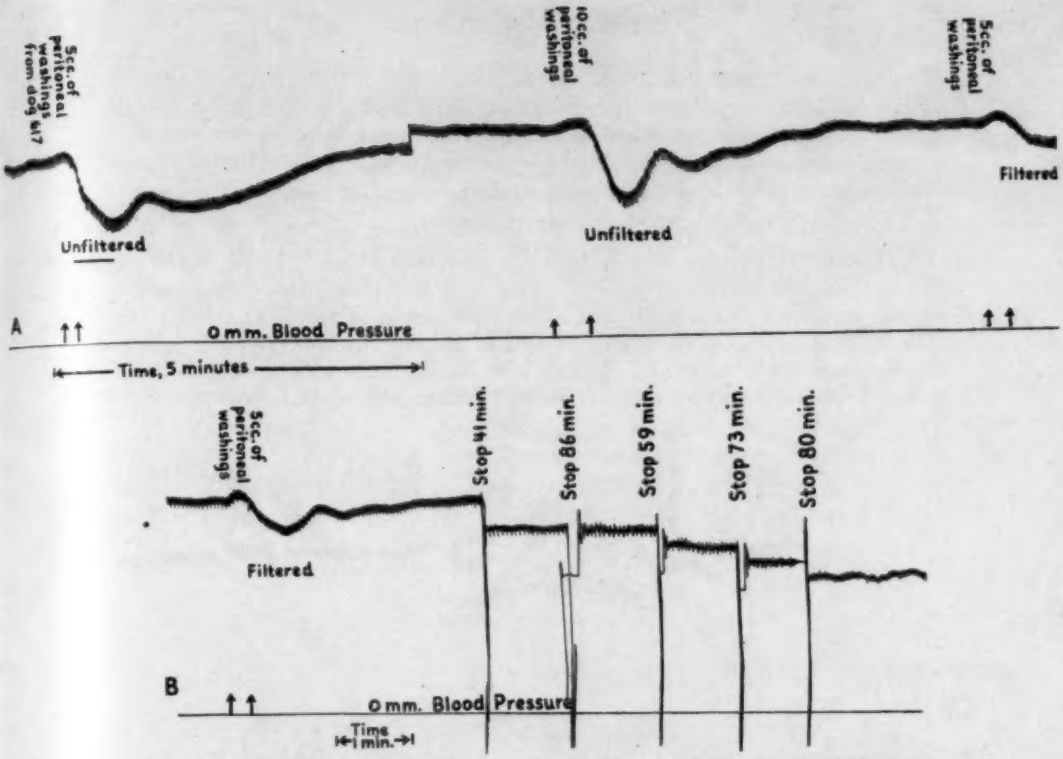

Chart 2.—The comparative effect on the blood pressure of centrifugated peritoneal washings from dog 617 from an open intestinal loop seventy-two hours after operation before and after passage through a Mandler filter. Blood pressure observations were made over six and one-half hours.

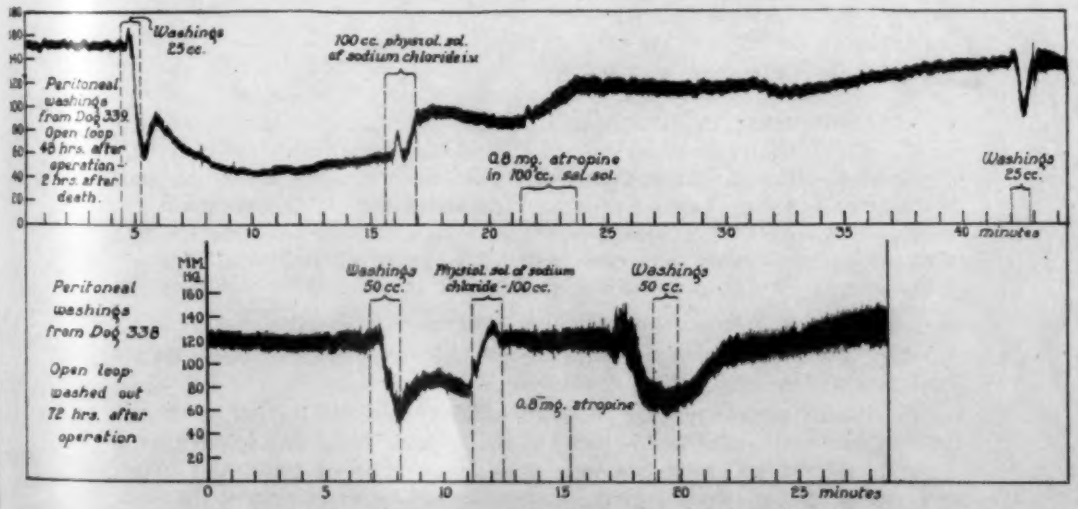
Washings 25 cc.
100 cc. physiol. sol. of sodium chloride iv
Peritoneal washings from Dog 339. Open loop 48 hrs. after operation - 2 hrs. after death.
0.8 mg. atropine in 100 cc. sal. sol.
Washings 25 cc.
minutes
MM. HG.
Washings 50 cc.
Physiol. sol. of sodium chloride - 100 cc.
Washings 50 cc.
Peritoneal washings from Dog 338
Open loop washed out 72 hrs. after operation
0.8 mg. atropine
minutes

Chart 3.—Comparison of vasodepressant action of centrifugated peritoneal washings before and after the administration of atropine. Blood pressure tracings from two dogs (338 and 339) each given an injection of peritoneal washings from a separate dog. Note variations in the drop in the blood pressures with the same test dose.

pared with the drop in blood pressure in other unatropinized animals (chart 4). In this particular experiment (peritoneal washings from dog 840) it can be seen that atropine sulfate completely abolished the reactivity of the vasomotor system to the depressant substance, regardless of whether it was given initially or after vasodepressant doses of the peritoneal washings.

EXPERIMENT 9.—*Symptoms produced by active fluids.*

(*a*) A vasodepressant fluid, of which 5 cc. caused a fall in blood pressure of 58 mm., was obtained from dog 617. This fluid was then injected intravenously without anesthesia into dogs 817 and 818 in quantities of 18 and 30 cc., respectively. Dog 817 had an emesis of about 150 Gm. of partially digested stomach contents ten minutes after injection and then appeared disinclined to walk around the room. Dog 818 seemed not to have been affected by the injection. Four hours after the

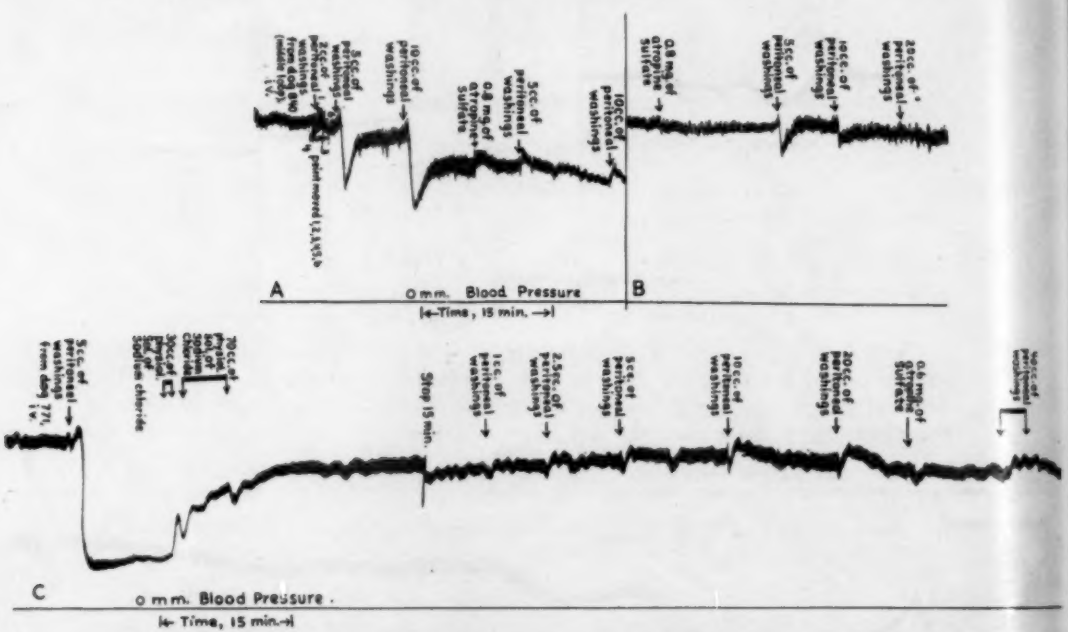

Chart 4.—Relation of varied time of atropinization to the effect on the blood pressure of active peritoneal washings. In *A* and *B* atropine sulfate practically abolished all reactivity of the vasodepressant substance, while in *C* the effect of atropine sulfate is uncertain because repeated injections of peritoneal fluid were without effect even prior to the administration of atropine.

injection both dogs appeared as before the material was administered and remained well over a four week period of observation.

(*b*) A similar vasodepressant fluid, of which 10 cc. caused a fall of 80 mm. in blood pressure, was obtained from dog 443. This fluid was then injected intravenously without anesthesia into three dogs in quantities of 10, 20 and 60 cc., respectively. The first two dogs appeared only unwilling to walk about the room, but the one receiving 60 cc. of the fluid had a large watery emesis twenty minutes after injection. Recurrence of emesis was noted frequently during the ensuing

ten hours. Sixteen hours after injection all three dogs appeared to be normal and were still well four weeks later.

EXPERIMENT 10.—*Blood pressure drop in unanesthetized animals.*

Twenty-three cubic centimeters of a peritoneal washing from dog 771, which in a previous experiment had caused a drop of 84 mm., was given intravenously to a normal unanesthetized dog. The blood pressure was recorded by puncture of the femoral artery. Prior to injection the blood pressure was 134 mm.; three minutes after injection it fell to 56 mm. The animal struggled for a few minutes and then became weak, but soon improved and was able to stand in twenty minutes. A loose stool was passed in the interim. A similar experience occurred with two other unanesthetized dogs treated in this way.

EXPERIMENT 11.—*Intraperitoneal injection of vasodepressant fluids.*

Toxic peritoneal washings were injected intraperitoneally into each of five dogs. Four were anesthetized with barbital and one with morphine and ether. Tracings from two of these animals are reproduced in chart 5, while chart 6 shows a record of the blood pressure of the animal anesthetized by morphine and ether.

TABLE 5.—*Hemoglobin Content and Hematocrit Readings on Dogs During the Development of Peritonitis*

Dog No.	Distance from Pylorus to Open Segment, Cm.	Interval (Hr.) Between		Hemoglobin Percentage (Sahli)		Hematocrit Reading (%)		Toxicity of Peritoneal Washings
		Operation and Lavage	Lavage and Death	Before Operation	After Peritonitis	Before Operation	After Peritonitis	
770	108	20	11	116	140	53	58	+
771	.4	27	0.25	96	128	42	50	+
775	6	17	3	102	106	47	52	0
776	128	20	18	118	130	50	54	+

From 5 to 15 cc. of the peritoneal washings obtained from dog 845 produced a drop of 34 and 36 mm., respectively, on intravenous administration. But a drop of only 20 mm. in one hundred and twenty-six minutes resulted from intraperitoneal injection of 40 cc. of the same fluid. The active peritoneal washing from dog 840 caused a drop of 8 mm. in sixty-six minutes. In another experiment 50 cc. of a peritoneal washing, of which 5 cc. caused a drop in blood pressure of 42 mm. on intravenous injection, caused a decline in blood pressure from 146 to 106 mm. in twenty-four minutes after intraperitoneal injection. Since there is a slight drop in blood pressure over such periods of time in certain barbitalized animals, another experiment (chart 6) was performed, morphine and ether anesthesia being used. Reference to this figure shows the unmistakable action of the vasodepressant substance after intraperitoneal administration.

EXPERIMENT 12.—*Fluid loss from the blood during development of experimental suppurative peritonitis.*

In four animals observations were made on the hemoglobin content and the percentage by volume of red blood cells during the development of peritonitis. These values are seen in table 5. Observations were not made on the blood pressure of these animals.

It is seen that during the development of peritonitis in these animals there is some slight concentration in blood, as evidenced by a slight rise in hemoglobin and hematocrit values. This change was not marked and can be easily accounted

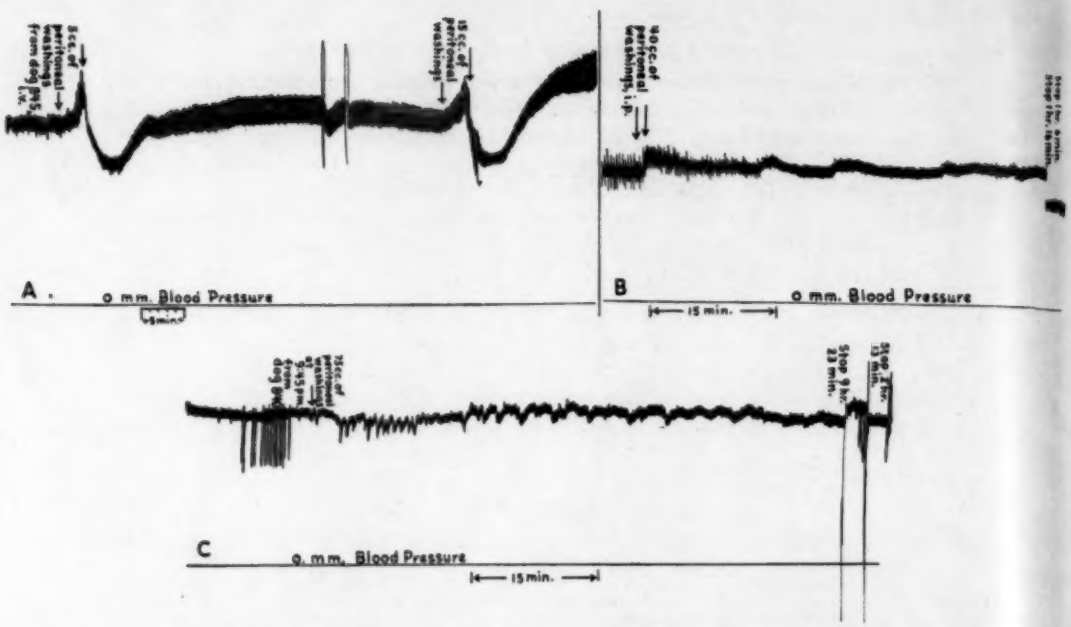

Chart 5.—Comparison of the vasodepressant effect of active peritoneal washings administered by various routes: *A*, intravenously; *B*, intraperitoneally and *C*, intraperitoneally. Although not reproduced in these tracings, the peritoneal washings from dog 840 were a potent preparation. Note the primary pressor effect with the washings from dog 845 in *B*.

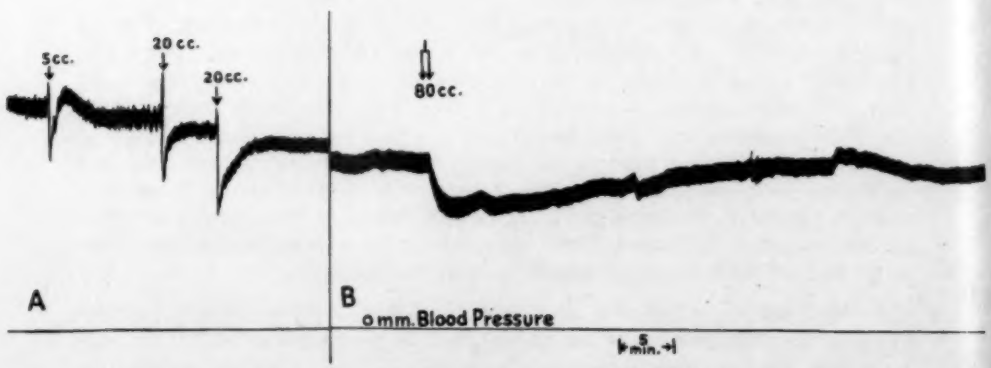

Chart 6.—Comparison of vasodepressant effects of active peritoneal washings given in varying doses (*A*) intravenously and (*B*) intraperitoneally. Note the sustained fall in bood pressure when the material was given by the latter route. (The test animal used for the intraperitoneal injection was given morphine-ether anesthesia.)

for by the emesis that occurred and by the fact that fluids were withheld. No significant amounts of fluid were seen within the abdominal cavities of these animals when they were opened for peritoneal lavage.

EXPERIMENT 13.—*Shock syndrome produced by active peritoneal fluids.*

Observations were also made on the blood pressure, the hemoglobin content, the percentage (by volume) of red cells and the bleeding volume in seven dogs that had received repeated intravenous injections of toxic peritoneal fluid sufficient to lower the blood pressure to a shock level. A record of these findings is given in table 6. It is seen that there was no significant change in the hemoglobin and hematocrit readings. The average bleeding volume obtained in terms of percentage of the calculated blood volume was 54.3. Such observations place the action of this substance in the category of primary shock analogous to the type induced by the administration of histamine.[24]

TABLE 6.—*Data on Blood Pressure, Bleeding Volume, Percentage (by Volume) of Red Cells and Hemoglobin Content of Dogs Receiving Active Peritoneal Washings Intravenously*

Dog No.	Weight, Kg.	Blood Pressure		Time (Min.) Between Initial Observation and Bleeding at Point of Low Blood Pressure	Time (Min.) Blood Pressure Remained at Shock Level (Below 80 Mm. Pressure)	Hemoglobin Percentage		Hematocrit Reading		Bleeding Volume	
		Initial	Prior to Bleeding			Initial	Prior to Bleeding	Initial	Prior to Bleeding	Cc.	Percentage of Calculated Blood Volume
767	5.5	122	68	12	5.5	104	106	43	43	228	53.9
813	6.5	126	62	29	16	78	92	35	38	270	54.0
816	6.0	134	46	23	10	82	106	41	46	265	57.5
817	7.5	154	34	37	20	118	120	51	50	210	57.7
818	5.0	138	80	32	13	108	98	43	44	215	55.9
819	7.0	130	72	59	9	92	92	42	40	247	46.1
820	6.0	126	26	14	5	80	82	40	..	255	55.3
Average bleeding volume (percentage of calculated blood volume), all experiments...											54.3

COMMENT AND SUMMARY

These experiments demonstrate the presence of a vasodepressant toxin occurring in the peritoneal cavity coincident with the development of suppurative peritonitis. The earlier experiments in this series (tables 1, 2 and 3) demonstrate clearly that a definite time is required for the development of this toxic product. The toxin or toxins seem to appear earlier when the open intestinal segment is placed high in the gastro-intestinal tract, where opportunity is greatest for soiling the upper portion of the abdomen. The nature of the experiments was such as to rule out effectively the possibility of inherent toxicity of the

24. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161, 1933.

pancreaticoduodenal secretion, a factor that has been recently demonstrated by Gatch and his co-workers.[18]

The identity of this toxic substance has not been fully elucidated in this series of experiments. It is highly probable in view of the variable response obtained on the blood pressure after atropinization that there is more than one substance involved. Either acetylcholine or a like substance is definitely present in certain of these preparations. Demonstration that these fluids lower the blood pressure in rabbits as well as in dogs is definite evidence that histamine is not the major substance involved. That some or all of these vasodepressant substances are filtrable through a bacteria-tight filter, that they are active on absorption from the peritoneum and that they lower blood pressure and produce symptoms of weakness and hypermotility of the gastro-intestinal tract in normal unanesthetized dogs is also demonstrated in these experiments.

It is well known that toxic amines can be obtained by extraction in saline solution from practically all the body tissues, including the peritoneum, after death. Our experiments were performed so as to obtain peritoneal washings many hours and at times even days prior to death from suppurative peritonitis. Thus, the question of agonal invasion has been avoided. It is noteworthy that cultures for bacteria gave a rich flora from the peritoneum in all our animals. The colon bacillus and a gram-positive spore-forming obligate anaerobic organism resembling the Welch bacillus were invariably reclaimed, and usually staphylococci and streptococci. The question would naturally arise as to whether these micro-organisms produced a vasodepressant toxin in their growth within the peritoneum. This is being investigated further. That the colon bacillus or its growth products may be the most important source of this toxic substance is suggested by the fact that the fluid from experimentally induced bile peritonitis is devoid of a vasodepressant substance even when the entire peritoneal exudate is injected intravenously into a test animal at the stage when gram-positive obligate anaerobic organisms can be easily cultured. However, if death occurs and the peritoneal fluid is removed even as soon as a half-hour after death, there is a vasodepressant toxin present. At this time the colon bacillus as well as the anaerobe can be cultured. The identification and significance of the anaerobe in bile peritonitis will be discussed elsewhere.[25] Further studies are also being made on the chemical nature of this vasodepressant substance.

The similarity of the action of this depressant substance and that obtainable from normal fecal material and from the contents of

25. Harmon, P. H., and Harkins, H. N.: Peritonitis: II. The Effect on Blood Pressure of Protein-Free Extracts of the Peritoneal Content and of Filtrates from Pure Cultures of Bacteria, Arch. Surg., this issue, p. 580.

obstructed bowel is striking. A comparison of our blood pressure tracings with those demonstrated by Gatch and his co-workers,[18] who dealt with the latter materials, reveals this marked similarity.

Our experiments do not elucidate the exact rôle that these toxic substances play in the fatal decline from suppurative peritonitis. It is generally believed that absorption is slowed from an inflamed peritoneum, especially if there is a fibrinous exudate present. With such a substance present within the peritoneum in large quantities, it is highly possible that some absorption can and does take place. So far as we can determine from the literature, this is the first adequate demonstration of the association of such a substance with peritonitis, although some relatively insignificant falls in blood pressure in animals in which the condition developed were reported by Steinberg and his co-workers [13] and a "toxic proteose" was mentioned by Whipple.[14]

CONCLUSIONS

A vasodepressant toxic substance in the exudate of experimental suppurative peritonitis is demonstrated, and the conditions for its presence are outlined.

No similar substance was demonstrated in the exudate of bile peritonitis prior to death, or in the normal peritoneum or the soiled peritoneum without diffuse suppurative inflammation.

These toxic fluids were still active after filtration through a bacteria-tight filter. Because of their action after atropinization of the test animal, it is probable that acetylcholine or a similar substance is present in some instances. Histamine is not a significant component of these fluids.

The picture of shock produced by these toxic peritoneal fluids is a primary type of shock, since the blood pressure may be low while the bleeding volume approximates that of normal animals.

PERITONITIS

II. THE EFFECT ON BLOOD PRESSURE OF PROTEIN-FREE EXTRACTS OF THE PERITONEAL CONTENT AND OF FILTRATES FROM PURE CULTURES OF BACTERIA

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In previous experimental studies on peritonitis, we demonstrated [1] a vasodepressant toxic substance in peritoneal washings. The washings from normal animals and from animals on which an extensive gastrointestinal operation had been done, as well as washings from animals with experimental bile peritonitis, were innocuous under the same experimental conditions. Since the vasodepressant toxin occurred in the exudate after death from bile peritonitis, we suspected that the colon bacillus or one of the large gram-positive obligate anaerobic organisms might be a possible source of the substance. This association of bacteria with the production of a toxic substance has been demonstrated by many authors [2] in experimental intestinal obstruction and in experi-

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Read in part before the Chicago Surgical Society, Feb. 7, 1936.

From the Douglas Smith Foundation and from the Service of Dr. Edmund Andrews, Department of Surgery, the University of Chicago.

1. Harmon, P. H., and Harkins, H. N.: Studies in Peritonitis: I. The Effect on Blood Pressure of the Peritoneal Content in Suppurative and in Bile Peritonitis, Arch. Surg., this issue, p. 565.

2. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Cause of Symptoms and Death, Arch. Int. Med. **15**:392 (March) 1915. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, J. Exper. Med. **17**:286 and 307, 1913. Dragstedt, L. R.; Moorehead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **14**:17, 1916; Intestinal Obstruction: An Experimental Study of the Intoxication in Closed Intestinal Loops, J. Exper. Med. **25**:421, 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, ibid. **30**:109, 1919. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, J. A. M. A. **79**:1581 (Nov. 4) 1922; Chemical Studies on Intestinal Intoxication, J.Biol. Chem. **52**:111, 1922. Foster, W. C., and Hausler, R. W.: Acute Intestinal Obstruction: III. Simple Obstruction, Arch. Int. Med. **36**:31 (July) 1925. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16**:606 (Feb.) 1928. Wangensteen,

(Footnote continued on next page)

mental acute pancreatic necrosis. It has likewise been known for a long time that the colon bacillus [3] and allied organisms [4] produce a toxic substance that brings about rapid death when administered to laboratory animals by the intravenous or the intraperitoneal route. When given by the oral route these substances are inactive,[5] except when obtained by special technical methods.[6] It remained for Steinberg and Ecker [7] to show that the lethal agent of the colon bacillus could be specifically neutralized by an antiserum. None of these investigators have pointed out the mechanism by which death occurs when these substances are given. Symptoms are produced by the intravenous injection of the alleged toxin of intestinal obstruction and the toxin of acute pancreatic necrosis that are similar to those obtained by the parasympathetic stimulants of the choline group.[8]

In a review of the bacteriologic literature, it was found that broth cultures of the Welch bacillus [9] and allied organisms [10] possessed a vaso-

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O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, ibid. **16**:1089 (May) 1928. Scott, H. G., and Wangensteen, O. H.: Effect of Intravenous Injections of Peritoneal Fluids Recovered from Dogs Dying from Experimental Strangulations, Proc. Soc. Exper. Biol. & Med. **29**:559, 1932. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, Arch. Surg. **28**:232 (Feb.) 1934.

3. Zinnser, H.; Parker, J. T., and Kuttner, A.: On Certain Poisonous Substances Produced in Bacterial Cultures, Proc. Soc. Exper. Biol. & Med. **18**:49, 1920.

4. Branham, S. E.: Toxic Products of Bacterium Enteritidis and of Related Microorganisms, J. Infect. Dis. **37**:291, 1925.

5. Dack, G. M.; Harmon, P. H., and Jarra, I.: Negative Results Obtained on Introducing Heat Killed Cultures of Salmonella Aertrycke and Salmonella Enteritidis into the Intestinal Tract of Monkeys and Other Animals, J. Prev. Med. **2**:461, 1928. Verder, E., and Sutton, C.: Is Salmonella Food Poisoning Caused by Living Bacilli or by Thermostable Toxic Products? J. Infect. Dis. **53**:262, 1933. Koessler, K. K., and Hanke, M. T.: Studies on Proteinogenous Amines: IV. The Production of Histamine from Histadine by Bacillus Coli Communis, J. Biol. Chem. **39**:539, 1919; XVIII. On the Production of Histamine, Tyramine and Phenol in Common Laboratory Media by Certain Intestinal Microorganisms, ibid. **59**:855, 1924.

6. Jordan, E. O., and Burrows, W.: The Production of Enterotoxic Substance by Bacteria, J. Infect. Dis. **57**:121, 1935.

7. Steinberg, B., and Ecker, E. E.: The Effect of Antiserum Against the Soluble Toxic Substance of Bacillus Coli in Bacillus Coli Peritonitis, J. Exper. Med. **43**:443, 1926.

8. Simonart, A.: On the Action of Certain Derivatives of Choline, J. Pharmacol. & Exper. Therap. **46**:157, 1932.

9. Kojima, K.: Ueber dem Chemismus der Toxinbildung durch den Bacterium phlegmonis emphysematosae, Frankel., Biochem. Ztschr. **128**:519, 1923.

10. Kojima, K.: Beiträge zur Erforschung der Rauschbanderreger, Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:170, 185 and 203, 1923. Kendall, A. I., and Schmitt, F. O.: Studies in Bacterial Metabolism: LXXXI. Physiological Action of Certain Cultures of the Gas Bacillus, J. Infect. Dis. **39**:250, 1926.

depressant effect. Such facts are not as yet established in investigations of toxic cultures of the colon bacillus unless one excepts the recent experiments of Imanaga,[11] who showed that cultures of colon bacilli produce intestinal paralysis. This author did not investigate the effect of his cultures on the blood pressure. In a further study of the vasodepressant substances associated with bacterial peritonitis, we have investigated their relation to the choline group of vasodepressants and the effect on the blood pressure of toxic filtrates from certain of the bacteria generally associated with suppurative peritonitis. Preliminary communications of the results of these investigations have already appeared.[12] A detailed account follows.

EXPERIMENTS

The method of Chang and Gaddum[13] was used in preparing protein-free extracts of various materials: the peritoneal washings from animals with suppurative peritonitis, the peritoneal exudate from animals with experimental bile peritonitis, autoclaved 10 per cent solutions of bile salts,[14] the centrifugated sediments obtained in clearing the first two mentioned materials by centrifugation for intravenous injection, the supernatant fluid obtained in the same way and the sediments obtained in centrifugating whole broth cultures of colon bacilli, streptococci and staphylococci prior to preparation of a Berkefeld filtrate from them. This method consists in adding an equal volume of 10 per cent trichloracetic acid to the fluid to be tested, or from 2 to 5 cc. of the acid to each estimated gram of solid material to be extracted. The mixture is allowed to stand with occasional stirring for from one to two hours and is then filtered through a Buchner funnel. The filter paper on the funnel is washed with from 5 to 20 cc. of 10 per cent trichloracetic acid. The filtrate is then shaken with ether four or five times in a separatory funnel, the ethereal layer being discarded. The water-clear lower layer is then concentrated by in vacuo distillation at from 37 to 40 C. to a 10 to 15 cc. volume (representing generally a fivefold to tenfold concentration by this method). The solution is then titrated to neutrality to congo red with tenth-normal sodium hydroxide. Precautions were taken in the instances of the fresh peritoneal washings and exudates to mix the fluid with trichloracetic acid immediately on removal from the animal's body to avoid possible disintegration or destruction of any vasodepressant substance.

These extracts were tested for their effect on blood pressure both in dogs and in rabbits, in comparison with the action of known amounts of acetylcholine solution. In all, forty-one extracts were prepared, and each was tested for its

11. Imanaga, H.: Experimentelle Untersuchungen über den Entstehungsmechanismus der Darmlähmung bei akuter diffuser Peritonitis, Deutsche Ztschr. f. Chir. **244**:156, 1934.

12. Harmon, P. H., and Harkins, H. N.: Depressor Substances in Peritonitis, Proc. Soc. Exper. Biol. & Med. **32**:6, 1934; Bleeding Volume in Experimental Colon Bacillus Intoxication, ibid. **32**:1144, 1935.

13. Chang, H. C., and Gaddum, J. H.: Choline Esters in Tissue Extracts, J. Physiol. **79**:255, 1933.

14. Armour's purified bile salts were used.

effect on at least two animals of each mentioned species both before and after atropinization. The sensitivity of each test animal was determined by a series of injections of acetylcholine, usually from 1 to 5 micrograms.[15] Although this was not pointed out by Chang and Gaddum, blank extracts prepared by substituting distilled water for the substance to be extracted gave a minor drop of blood pressure in rabbits of from 4 to 5 mm., the equivalent of 0.05 microgram of acetylcholine. There was no difficulty, however, in selecting the extracts that gave a vasodepressant action, since the reactions were of the magnitude of from 1 to 5 micrograms per cubic centimeter, as expressed in terms of acetylcholine equivalents.

The vasodepressant action of these extracts paralleled the activity of the original materials tested; that is, whenever the vasodepressant toxin was present in the original material, the corresponding extract also contained a vasodepressant substance. About a third decrease in activity was noted after atropinization, thus showing the presence of acetylcholine. Extracts prepared from centrifugated sediments from both bacterial peritonitis and from bile peritonitis contained especially large quantities of vasodepressant substance, averaging from 1 to 2 acetylcholine equivalents per cubic centimeter. Here, again, the activity was only partially abolished after atropinization. The extracts from centrifugated fluids from all the instances of bile peritonitis were innocuous, similar to the effect of the original material. The original partially purified bile salt solution used in these experiments yielded a potent vasodepressant substance on extraction. None of the extracts prepared from bacterial sediments had a vasodepressant effect in these tests. The blood pressure of the rabbit was found to be a more sensitive indicator of small amounts of vasodepressant substance than that of the dog.

Since our earlier experiments pointed to the probable close relationship of the colon bacillus in the production of the vasodepressant substance, we have carried out tests on the effect of bacteria-free filtrates from broth cultures of this organism. We have extended these observations to other aerobic organisms, such as streptococci and staphylococci, as well as certain of the gram-positive spore-forming anaerobes, all frequently cultured from the peritoneal content in suppurative peritonitis. The actual source of these organisms varied: Of eleven strains of colon bacilli, eight were from urine obtained at cystoscopy and one was from pus obtained in a case of clinical peritonitis, one from the wall of the gallbladder in a case of chronic cholecystitis and one from a subcutaneous infection of the wound; of two strains of Streptococcus haemolyticus, one was obtained in a case of streptococcic peritonitis and another in a case of acute mastoiditis; one strain of Streptococcus viridans was isolated from urine; two strains of Staphylococcus aureus were isolated from subcutaneous abscesses. The identity of these strains of colon bacilli was verified by carbohydrate fermentations. Two strains of Clostridium Welchii and a strain each of Clostridium sporogenes, Clostridium Chauvei and Vibrio septicus had been carried as identified stock cultures in the laboratory for several years.

In the case of the aerobic organisms, 200 cc. of peptone-free veal infusion broth was inoculated with 2 cc. of a heavy twenty-four hour broth culture of the organism and set aside in the incubator for from four to twenty days. Anaerobic cultures were made by the usual technic in deep tubes containing dried beef heart overlayed with 20 cc. of the same peptone-free veal infusion broth. These cultures were sealed with petrolatum. At the end of the incubation periods these small quantities of culture were pooled for each organism, centrifugated for one hour at high speed and then passed through a sterile Berkefeld N filter. Filtration was repeated in the instance of the aerobic organisms in order to insure a bacteria-free

15. A microgram is 0.001 mg., or 0.000001 Gm.

filtrate. Cultures of these filtrates remained sterile. Portions of them were then tested on the blood pressure of dogs under anesthesia induced by either barbital, from 250 to 275 mg. per kilogram, or ethyl carbamate (urethane), 1.5 Gm. per kilogram. Observations were made on the blood pressure of control dogs by the intravenous injection of peptone-free veal infusion broth.

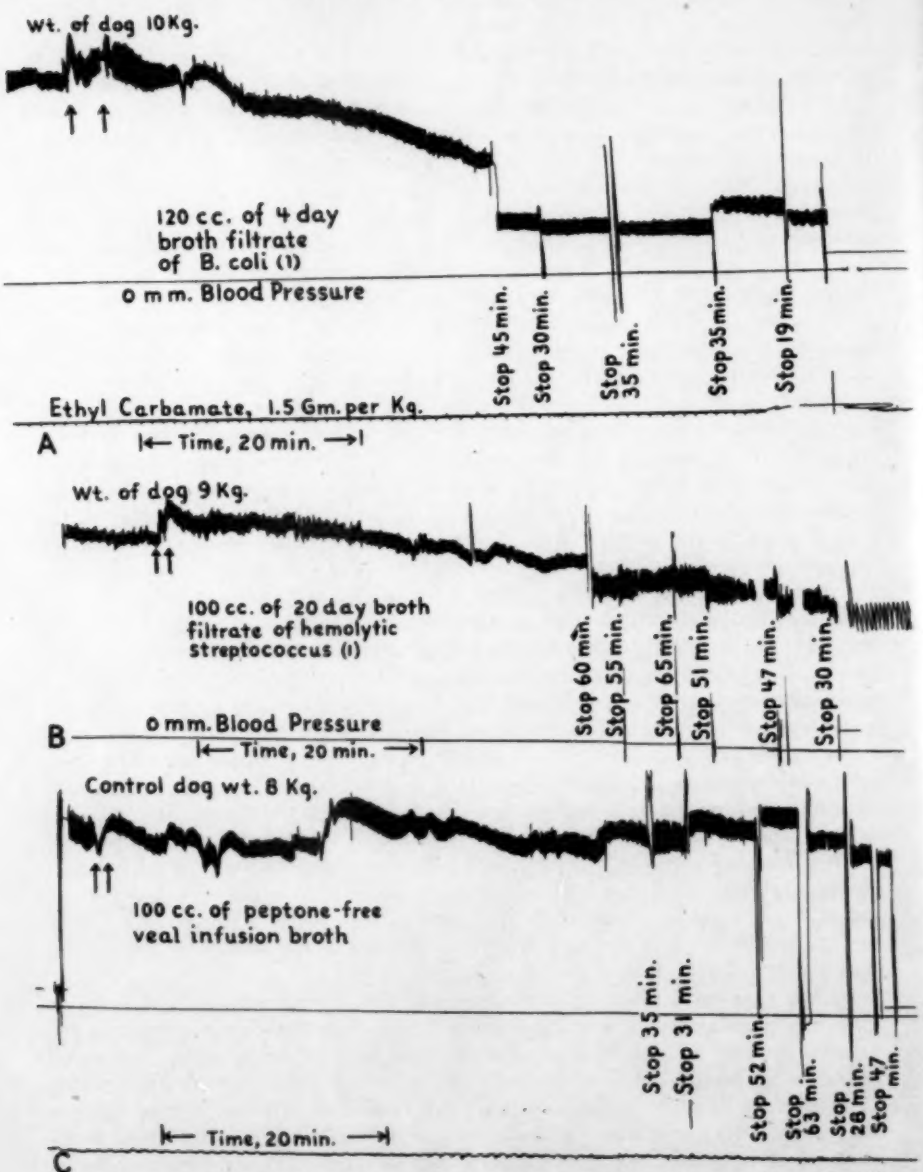

Chart 1.—Comparison of the effects of bacteria-free filtrates from aerobic organisms on blood pressure. *A* shows the effect of a filtrate of a four day culture of colon bacilli; *B*, the effect of a filtrate of hemolytic streptococcus and *C*, the effect of peptone-free veal infusion broth administered intravenously to a control dog. Note the marked vasodepressant effect of colon bacillus filtrate in *A*.

When filtrates of the colon bacillus were given intravenously (charts 1 and 2 and table 1), there was a slow decline in the blood pressure to a shock level, from thirty minutes to two or three hours being required for the minimal level to

TABLE 1.—*Effect of Sterile Filtrates from Certain Aerobic Bacteria on Blood Pressure in the Dog*

Organism and Source	Age of Culture, Days Prior to Filtration	Quantity Used for Test, Cc.	Effect on Blood Pressure; Drop (Mm. of Hg) from Average Initial to Average Final Reading
B. coli-1 (dog with peritonitis).....	4	100	Profound delayed drop
B. coli-1 (dog with peritonitis).....	8	80	Profound delayed drop
B. coli-1 (dog with peritonitis).....	20	100	B. P. 100-90 in 2 hr.
B. coli-2 (cystoscopic urine).....	4	90	B. P. 168-70 in 1½ hr.
B. coli-2 (cystoscopic urine).....	20	90	B. P. 126-70 in 20 min.
B. coli-3 (chronic cholecystitis).....	7	35	B. P. 158-32 in 1½ hr.
B. coli-4 (cystoscopic urine).....	7	100	B. P. 154-46 in 1½ hr.
B. coli-5 (cystoscopic urine).....	7	50	B. P. 126-42 in 2 hr. with death
B. coli-6 (cystoscopic urine).....	7	40	B. P 146-58 in 3 hr. with death
B. coli-7 (cystoscopic urine).....	7	50	B. P. 164-40 in 8¼ hr.
		43	B. P. 132-52 in 1½ hr.
B. coli-8 (cystoscopic urine).....	7	50	B. P. 166-42 in 2 hr.
		33	B. P. 162-82 in 2¼ hr.
B. coli-9 (wound infection).....	7	50	B. P. 124-36 in 2¼ hr.
		40	B. P. 148-54 in 2 hr.
B. coli-10 (cystoscopic urine).....	7	40	B. P. 164-66 in 2 hr.
B. coli-11 (cystoscopic urine).....	7	50	B. P. 134-38 in 5½ hr.
Str. haemolyticus-1 (streptococcic peritonitis)	2	120	Immediate drop in blood pressure of 40 mm. (no delayed drop)
Str. haemolyticus-1 (streptococcic peritonitis)	4	140	B. P. 112-80 in 6 hr. 40 mm. (no delayed drop)
Str. haemolyticus-1 (streptococcic peritonitis)	8	80	B. P. 160-140 in 4 hr.
Str. haemolyticus-2	4	100	B. P. 140-120 in 6 hr.
	20	75	Profound immediate drop with rapid recovery; no late drop
Str. viridans (cystoscopic urine)....	4	100	B. P. 102-110 in 7 hr.
Str. viridans (cystoscopic urine)....	20	90	B. P. 152-134 in 3 hr.
Staph. aureus-1 (abscess).....	4	100	B. P. 118-114 in 8 hr.
Staph. aureus-1 (abscess).....	20	55	Profound immediate drop with rapid recovery; no late drop
Staph. aureus-2 (abscess).....	4	100	B. P. 100-72 in 6 hr.
Staph. aureus-2 (abscess).....	20	100	B. P. 108-90 in 5 hr.
Uninoculated peptone-free veal infusion broth (control)	..	100	No change in blood pressure
	..	100	B. P. 124-114 in 6 hr.
	..	120	B. P. 116-90 in 9 hr.
	..	130	B. P. 113-110 in 3 hr.
	..	200	B. P. 146-130 in 3 hr.
	..	200	B. P. 110-90 in 5 hr.

be reached. In most instances death occurred after several hours with a depressed blood pressure. An illustrative experiment is reproduced in tracing *A* of chart 1. In this instance a 10 Kg. dog was given an intravenous injection of 120 cc. of a

filtrate from a four day culture of colon bacilli. The initial blood pressure of 122 mm. gradually declined to 34 mm. in one hundred minutes. The animal died three hours and forty minutes later. There was no case of an immediate drop in the blood pressure in tests of these filtrates of colon bacilli (eleven strains tested in seventeen dogs), but in every instance there was a profound delayed drop in the blood pressure to a shock level (table 1). The results of the intravenous injection of filtrates of colon bacilli into two other dogs are shown in chart 2.

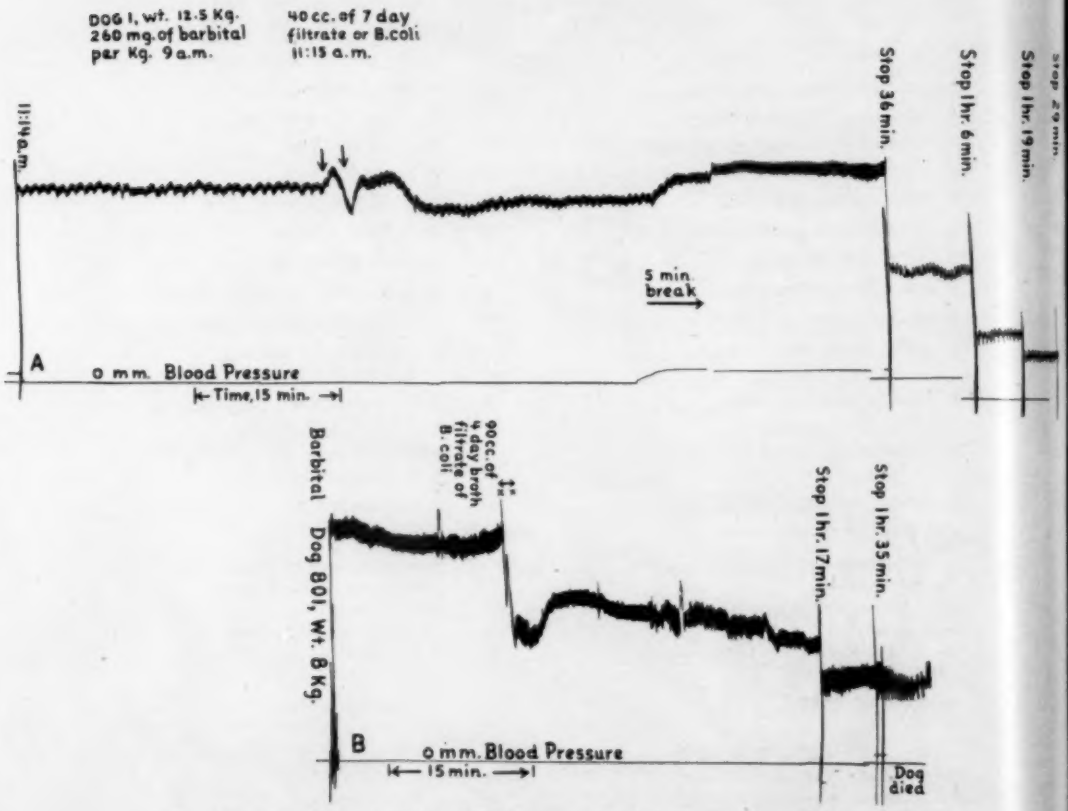
DOG I, wt. 12.5 Kg.
260 mg. of barbital per Kg. 9 a.m.
40 cc. of 7 day filtrate of B.coli 11:15 a.m.
11:14 a.m.
Stop 36 min.
Stop 1 hr. 6 min.
Stop 1 hr. 19 min.
5 min. break
A
0 mm. Blood Pressure
Time, 15 min.
Barbital
Dog 801, Wt. 8 Kg.
90 cc. of 4 day broth filtrate of B. coli
Stop 1 hr. 17 min.
Stop 1 hr. 35 min.
B
0 mm. Blood Pressure
15 min.
Dog died

Chart 2.—Tracings showing the effect on the blood pressure of other peptone-free veal infusion broth filtrates of colon bacilli, given intravenously.

Six of the fourteen filtrates of colon bacilli were tested by intravenous injection into unanesthetized rabbits after the method of Steinberg and Ecker [7] for determining the presence of the "soluble specific substance" of the colon bacillus. All six of them in quantities of 5 cc. produced weakness, diarrhea, collapse and convulsions. Four of six animals succumbed.

In the tests of filtrates from streptococci and staphylococci, there was a slight (average of eight tests 16.5 mm.) delayed drop in blood pressure, but this was not significantly greater than that for the six control animals receiving peptone-free veal infusion broth intravenously (average fall in blood pressure 12.5 mm.). In three instances there was a profound immediate drop in the blood pressure as a

result of the intravenous injection of such products. Two of these three instances occurred when filtrates from twenty day cultures were tested (chart 3). In these latter three instances there was no delayed drop in the blood pressure.

An inquiry into the mechanism of the drop in blood pressure and the shock syndrome so produced was next carried out. Hemoglobin and hematocrit observations were made on dogs receiving such filtrates in conjunction with the blood pressure observations. After the blood pressure had declined to the shock level, the bleeding volume[16] was determined.

It is seen from these observations (table 2) that the average bleeding volume after the intravenous injection of colon bacillus filtrate was 46 per cent of the calculated blood volume. Since the average normal bleeding volume was found to be 58.6 per cent by Roome, Keith and Phemister and 53.4 per cent by one of us (H. N. H.),[17] our findings allow the fall in blood pressure that occurs after the intravenous administration of a filtrate of colon bacillus to be classed as primary shock.

TABLE 2.—*Terminal Bleeding Volume; Associated Changes in Blood Pressure, Cell Volume and Hemoglobin Content After the Intravenous Injection of Colon Bacillus Filtrates*

Dog No.	Weight, Kg.	Berkefeld Filtrate Intravenously	Time from Injection to Death by Bleeding, Hr.	Blood Pressure		Hemoglobin Percentage		Hematocrit Reading		Terminal Bleeding Volume, Percentage of Calculated Blood Volume
				Initial	Prior to Bleeding	Initial	Prior to Bleeding	Initial	Prior to Bleeding	
1P	6.0	50 cc. B. coli-communis (Sw)*	2.0	166	42	84	94	38	45	43
2P	7.5	50 cc. B. coli-communior (St)	5.5	...	..	105	112	48	55	52
3P	7.5	50 cc. B. coli-communior (Di)	2.25	124	36	100	122	45	58	33
4P	5.0	50 cc. B. coli-communis (Ja)	8.25	164	40	91	105	46	50	61
5P	8.8	40 cc. B. coli-communior (La)	2.0	164	66	104	106	45	45	35
1002	8.6	43 cc. B. coli-communis (Ja)	1.5	132	52	122	118	51	54	49
1003	8.0	40 cc. B. coli-communior (Di)	2.0	148	54	128	126	53	53	49
		Average								46

* Laboratory designation of strain.

The significance of such falls in blood pressure is magnified, provided that the action can also be demonstrated after the intraperitoneal administration of the same products. The blood pressure records of four tests are reproduced in chart 4. A drop in blood pressure occurred in each of the four animals but was significant in but one.

Two filtrates from each of five cultures of obligate anaerobic organisms were tested on the blood pressure of dogs. No delayed fall in blood pressure occurred in forty tests on the blood pressure of ten dogs. All the effects observed were

16. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161, 1933.

17. Harkins, H. N.: Bleeding Volume in Experimental Burns, Proc. Soc. Exper. Biol. & Med. **32**:3, 1934.

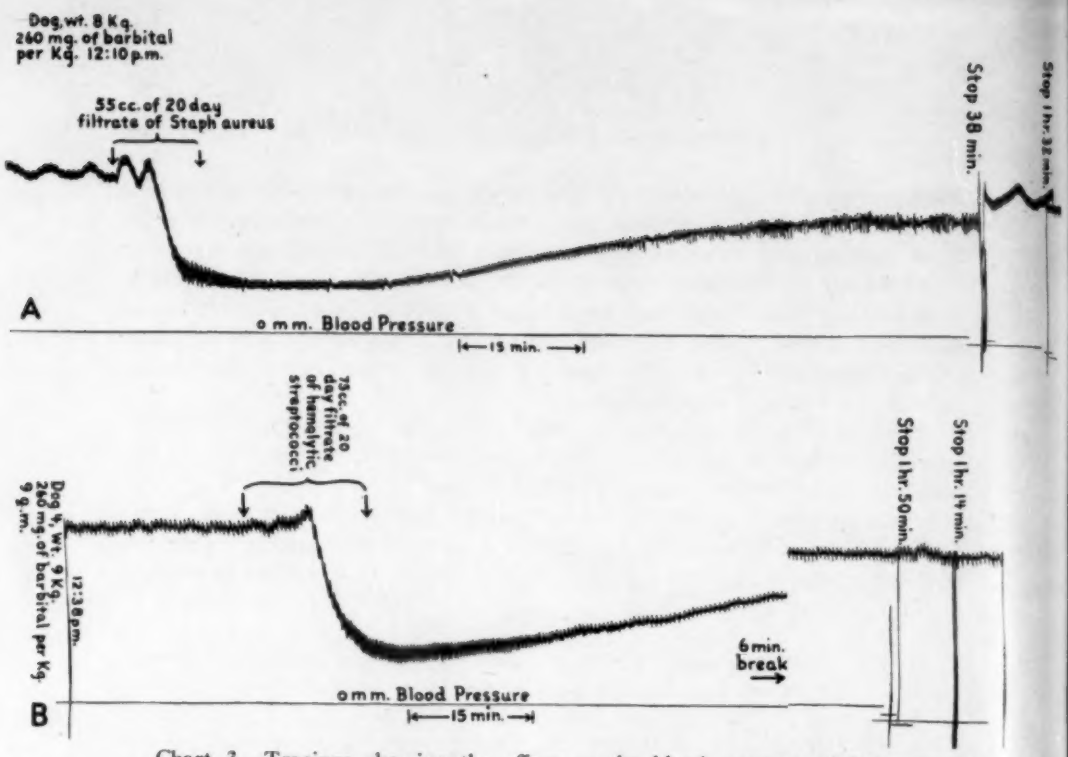

Chart 3.—Tracings showing the effect on the blood pressure of intravenous bacteria-free filtrates. In *A* a filtrate of staphylococci was used, and in *B*, a filtrate of hemolytic streptococci. Note the profound immediate drop with slow recovery in each case.

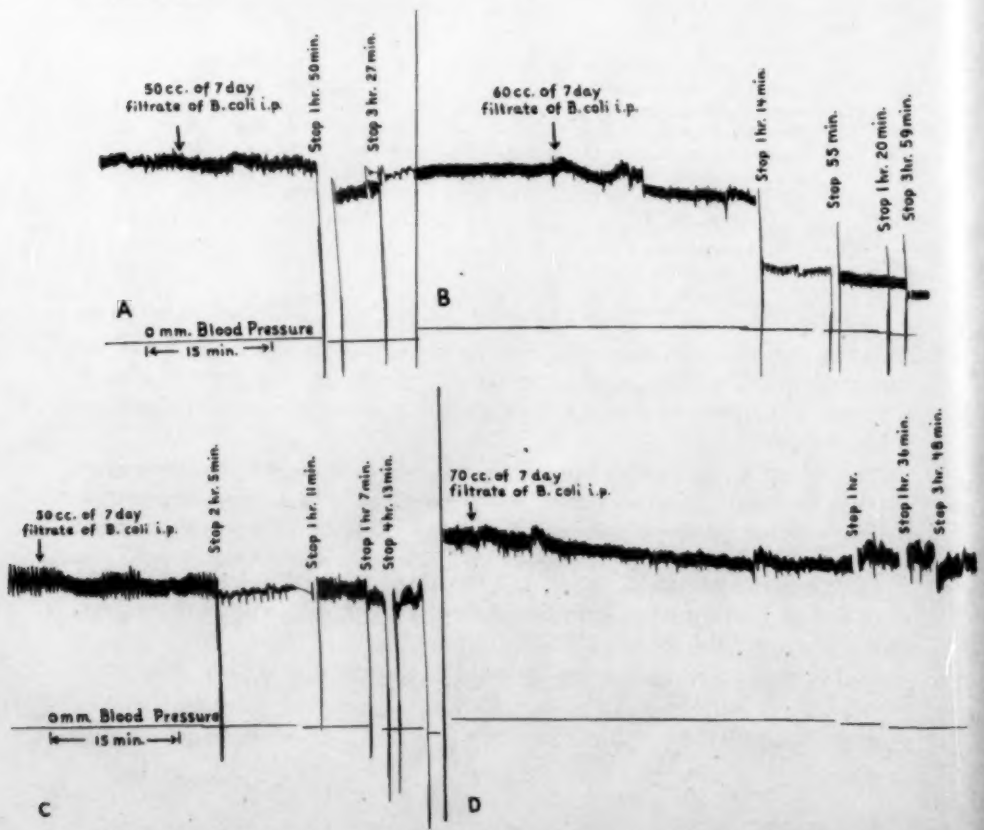
50 cc. of 7 day
filtrate of B. coli i.p.
Stop 1 hr. 50 min.
Stop 3 hr. 27 min.
60 cc. of 7 day
filtrate of B. coli i.p.
Stop 1 hr. 19 min.
Stop 55 min.
Stop 1 hr. 20 min.
Stop 3 hr. 59 min.
A
o mm. Blood Pressure
15 min.
B
50 cc. of 7 day
filtrate of B. coli i.p.
Stop 2 hr. 5 min.
Stop 1 hr. 11 min.
Stop 1 hr 7 min.
Stop 4 hr. 13 min.
70 cc. of 7 day
filtrate of B. coli i.p.
Stop 1 hr.
Stop 1 hr. 36 min.
Stop 3 hr. 48 min.
o mm. Blood Pressure
15 min.
C
D

Chart 4.—Tracings showing that vasodepression occurs after the intraperitoneal administration of bacteria-free colon bacillus filtrates. The effect is most pronounced in the upper tracing (*B*).

immediate. Chart 5 is a reproduction of representative blood pressure tracings illustrating the effect of these filtrates. The preparations from Cl. Chauvei and from Vibrio septicus were devoid of action on the blood pressure, while filtrates from two different cultures of Cl. Welchii and from a culture of Cl. sporogenes possessed a powerful vasodepressant action. In collateral experiments this same vasodepressant action was demonstrated in rabbits. This effect was also found to persist after atropinization in both rabbits and in dogs.

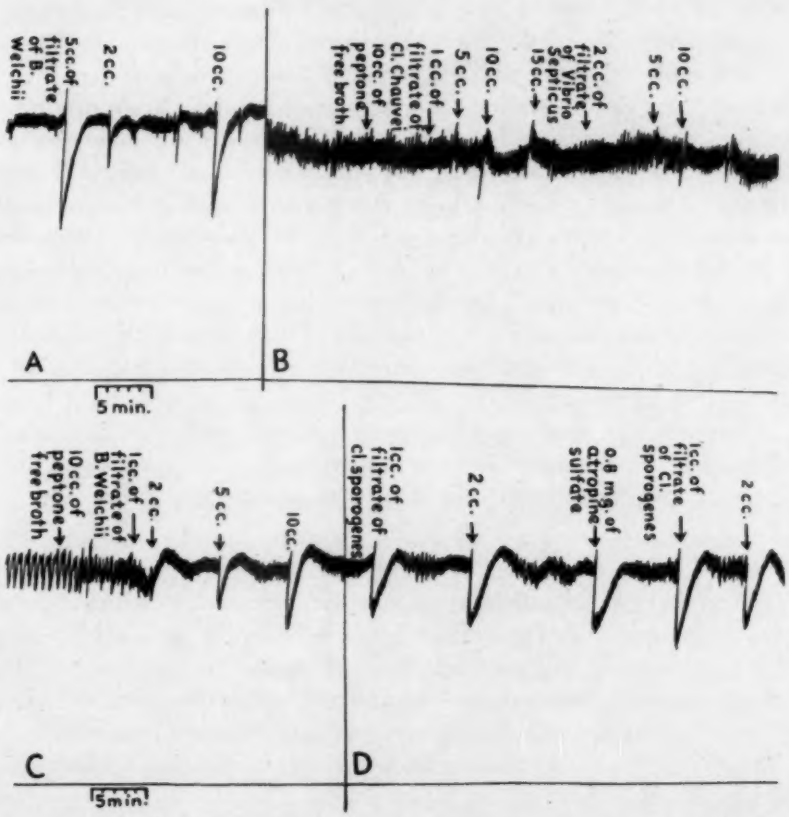

Chart 5.—Tracing showing the effect on the blood pressure of the intravenous administration of bacteria-free filtrates of anaerobic bacilli. In *A* a filtrate of Cl. Welchii was used; in *B*, of Cl. Chauvei and Vibrio septicus; in *C*, of Cl. Welchii, and in *D*, of Cl. sporogenes.

COMMENT AND SUMMARY

These experiments constitute an inquiry into the nature and origin of the toxic substance present in the peritoneal cavity in experimental suppurative peritonitis. They demonstrate that the substance is not a protein since it occurs in the filtrate after treatment with trichloracetic acid. Similar extracts of the centrifugated sediments yielded protein-

free filtrates of particular potency. Such a finding points to the cellular abdominal débris, composed of polymorphonuclear phagocytes and adherent material, as being the fraction most potent in the substance. Since similar extracts of washed bacteria were strikingly free from vasodepressant action, it would appear that the substance is a soluble toxin. Its close association with peritoneal cellular débris may indicate either absorption of the toxin to such cells or that the substance is a product of them. Tests of the bacteria-free filtrates from pure cultures of bacteria were included. Even though the symptoms produced by the soluble specific substance of Steinberg and Ecker have been long known, this is the first demonstration that the same bacterial filtrate produces a profound vasodepression. It is possible that the symptoms produced by the soluble specific substance are only those due to the low blood pressure. The close relationship of symptoms to vasodepression is further indicated, as both have an appreciable incubation period following injection before the onset of symptoms. These experiments also demonstrate that certain of the spore-forming obligate anaerobes and staphylococci and streptococci, all organisms associated with suppurative peritonitis, produce soluble vasodepressant substances that appear in bacteria-free filtrates.

The exact rôle that these substances play in an actual instance of peritonitis is not elucidated in these experiments. It is not inconceivable that they could contribute to the final fatal decline in this disease.

CONCLUSIONS

The toxic vasodepressant substance that is present in the peritoneum in many instances of experimental suppurative peritonitis is nonprotein in nature and occurs in greatest concentration in extracts prepared from the centrifugated sediment obtained from peritoneal washings.

The soluble toxic substance present in bacteria-free filtrates of colon bacillus produces a powerful vasodepression after an incubation period following its injection.

The toxic substance from this organism is similarly active after intraperitoneal injection in some instances.

By the bleeding volume method and by observations on cellular and hemoglobin concentration in the blood, the shock syndrome produced by administration of toxic filtrates of the colon bacillus was found to be a primary type, analogous to that produced by the experimental injection of other vascular poisons such as histamine.

Vasodepressant substances with an almost immediate time of action are also produced by the staphylococcus, by strains of streptococci and by cultures of the Cl. Welchii and Cl. sporogenes that we have examined.

USE OF EXTRAVASATING DYE AS A MEASURE OF SKIN PERMEABILITY TO BACTERIAL INVASION

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AND
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The subject of disinfection of the skin divides itself naturally into two categories: The first treats of the various chemical or physical means by which the skin is rendered sterile, in other words, the surgical disinfectants, and the second treats of the disinfective power of the skin itself. It is with the latter aspect that this study is concerned.

Colebrook and his co-workers [1] and Arnold [2] have conclusively shown that the epidermis not only acts as a mechanical barrier against invading organisms but maintains its own indigenous flora and prevents the percutaneous penetration of foreign bacteria. Arnold [2b] demonstrated that exogenous bacteria and other antigenic substances penetrated into the stratum corneum, where by some unknown process they were either inactivated or destroyed. Tracing the fate of the vanished bacteria in the stratum corneum by the injection of scrapings of keratinized epithelium into animals, he was able to show the presence of their antigens by the recovery of antibodies. Control experiments carried out on the skin of cadavers failed to demonstrate the rapid disappearance of the same organisms.

Other methods of investigating the self-disinfecting property of the skin and determining the presence and degree of percutaneous bacterial invasion have been carried out by Brann [3] and Fleming,[4] who determined the bactericidal effect of cutaneous extracts and other tissues. The percutaneous penetration of antigens has been well established by

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From the Laboratory of Surgical Research, Harvard Medical School.

1. Colebrook, L., in Interim Report of Department Committee on Maternal Mortality and Morbidity, London, His Majesty's Stationery Office, 1930, appendix D, p. 132.

2. (*a*) Arnold, L., and others: Am. J. Hyg. **11**:345, 1930. (*b*) Arnold, L., and Bart, A.: ibid. **19**:217, 1934.

3. Brann, G.: Klin. Wchnschr. **7**:2059, 1928.

4. Fleming, A.: Lancet **1**:217, 1929.

Kolle,[5] Manfredi and Frisco,[6] Martini,[7] Hoffmann,[8] Fränkel[9] and Hardy, Hudson and Jordan.[10] The criteria used by these investigators for the penetration of bacteria were active systemic disease, positive results of blood culture or demonstrable antibodies. Hallwachs,[11] Kasten,[12] Sato[13] and Matsumoto and Shiraiwa[14] were not uniformly successful in proving this penetration. The discrepancies and their results can perhaps be explained on an increased resistance of the skin to permeation. The work of Arnold implies that the defensive power resides in the stratum corneum, and injuries to it, such as minute abrasions which are incurred in shaving, may increase the permeability of the skin, as has been confirmed by the work of Hardy, Hudson and Jordan.[10]

While results in the literature proved suggestive, we felt that the methods used did not afford a very exact evaluation of percutaneous bacterial invasion as an active process. We thus found it necessary in our investigation: (1) to measure the degree and presence of percutaneous bacterial invasion; (2) to determine how rapidly the self-disinfecting power is restored to the shaven skin and (3) to determine if shaving modifies the intracutaneous spread of bacteria.

GENERAL CONSIDERATIONS AND MATERIALS

It is known that local infection alters the capillary permeability in the process of forming inflammation. Induration, edema and erythema are unquestionably derived from the capillaries themselves. It occurred to us that should the capillary blood be colored by a dye, the resulting transudate or exudate would then likewise be colored. Bacterial invasion with subsequent inflammation would result in extravasation of a circulating dye. The advantage of the dye in this case would be that the slightest inflammation would be sharply outlined, whereas a slight degree of erythema under ordinary conditions is difficult to observe and delimit.

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5. Kolle, W.: Ztschr. f. Hyg. u. Infektionskr. **36**:397, 1901.
6. Manfredi, L., and Frisco, B.: Centralbl. f. Bakt. **32**:295, 1902.
7. Martini, E.: Ztschr. f. Hyg. u. Infektionskr. **41**:153, 1902.
8. Hoffmann, W.: Hyg. Rundschau **13**:114, 1903.
9. Fränkel, C.: Hyg. Rundschau **17**:903, 1907.
10. Hardy, A. V.; Hudson, M. G., and Jordan, C. F.: J. Infect. Dis. **45**:271, 1929.
11. Hallwachs, W.: Ztschr. f. Hyg. u. Infektionskr. **69**:149, 1911.
12. Kasten, F.: Deutsche med. Wchnschr. **26**:637, 1903.
13. Sato, K.: Jap. J. M. Sc. Tr., VII, Social Med. & Hyg. **1**:175, 1932.
14. Matsumoto, K.; Matsumoto, O. K., and Shiraiwa, T.: Sc. Rep., Govt. Inst. Infect. Dis., Japan **6**:145, 1927.

At the suggestion of Dr. John G. Gibson II, of the Peter Bent Brigham Hospital, we employed the blue azo dye T-1824 used by Gregersen and Gibson [15] in the determination of plasma volume. This dye (not listed in the "Color Index") was first used by Dawson, Evans and Whipple.[16]

The first indication of the property of this dye to extravasate only where there is increased vascular permeability was noted by Gibson in the course of determining the plasma volume of a patient undergoing fever therapy with diathermy. He observed that the serum contained in a blister caused by an accidental burn was colored blue. Analysis of this fluid in the bleb showed that the ratio of dye concentration to serum protein was identical with that in the blood plasma of the patient. Further observations made by Gibson indicate that this dye, when injected intravenously, enters into some form of combination with serum proteins and that in this combined state it does not permeate the normal capillary wall. He has found that changes in capillary permeability which allow the passage of serum protein through the endothelium also permit the escape of the dye. In short, in the case of the bleb caused by a burn the capillaries at this point were so altered by an irrational phenomenon as to allow the escape of serum proteins together with the dye.

METHOD

In our studies we produced such an irritation to the capillaries of the skin by subjecting them to bacterial invasion. Animals were used in which an excess of dye was in circulation, but in which the skin had not assumed the generalized blue color. One and five-tenths cubic centimeters of the blue azo dye T-1824 (0.5 Gm. per hundred cubic centimeters in saline solution) which had been sterilized was injected into a vein in the margin of the ear of each rabbit twenty-four hours previous to any experiment.

Several series of healthy domestic brown rabbits of the cottontail variety were used. In each instance the abdomen was shaved carefully in order to avoid traumatic abrasions. The skin was then washed with physiologic solution of sodium chloride and with water and subsequently dried.

Standardized eighteen hour broth cultures (p_H 7.4) of Streptococcus haemolyticus (beta) were used. In each instance a fresh culture was so prepared that at the time of application to the skin it had been incubated for eighteen hours after the initial seeding of the broth. The same strain of organisms was used throughout the experiments. Two cubic centimeters of this culture was applied with a cotton swab to the shaven skin of a rabbit.

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15. Gregersen, M., and Gibson, J.: Am. J. Physiol. **50**:113, 1935.

16. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: Am. J. Physiol. **51**:232, 1920. The dye is orthotoluidine combined with 2 mols of 1.8 amino 2.4 disulfonic acid. The lot employed in the work was synthesized by the Eastman Kodak Company according to the preparation and directions of Mr. Fieser and Mr. Hartwell, of the Department of Chemistry, Harvard University.

To study variations of intracutaneous spreading of bacteria, a solution containing a substance which we shall call, for purposes of abbreviation, the Reynals factor was prepared from freshly ground testicle. The method was fully described in the reports of the previous investigations by Duran-Reynals [17] and by one of us (M. P.[18]).

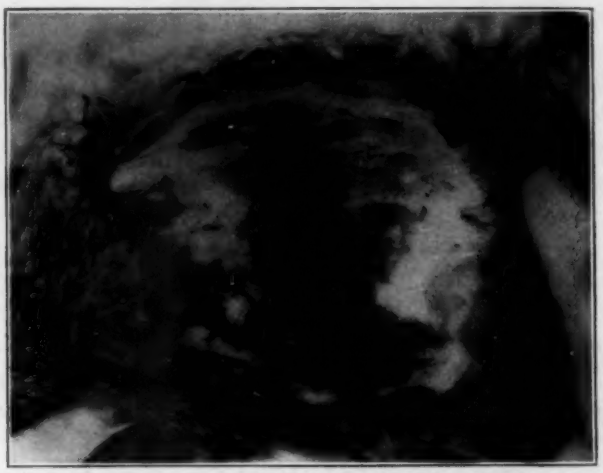

Fig. 1.—Extravasation of dye and areas of hemorrhage occurring in skin in which the bacteria were applied eighteen hours after shaving. Interval: ten hours after application of organisms.

Fig. 2.—Early extravasation of dye occurring in skin in which the bacteria had been smeared twenty-four hours after shaving. Interval: six hours after application of organisms.

EXPERIMENTAL DATA

Percutaneous Invasion of Streptococci.—Eight rabbits with abdomens carefully shaved were swabbed at various intervals with an eighteen hour broth culture

17. Duran-Reynals, F.: J. Exper. Med. **50**:327, 1929.

18. Pijoan, M.: J. Exper. Med. **53**:37, 1931.

of Str. haemolyticus (beta). In each instance an area of 5 by 10 cm. on the abdomen of the rabbit was uniformly smeared with 2 cc. of this culture. In table 1 are recorded the extent of the lesion and the degree of percutaneous invasion in rabbits shaved at approximately the same time but swabbed at various intervals.

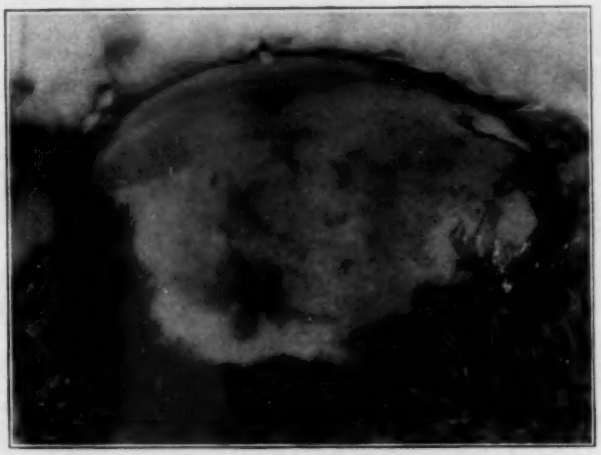

Fig. 3.—Extravasation of dye in skin on which the bacteria were applied thirty-five hours after shaving. Interval: ten hours after application of organisms.

Fig. 4.—Absence of extravasation of dye in skin on which the bacteria were applied forty hours after shaving. Interval: ten hours after application of organisms.

It was further noted that after the extravasation had taken place the blue dye remained fixed in the inflamed tissues, with no appreciable fading. The striking appearance of the dye-stained tissues is clearly shown in the photographs. Controlled experiments with dye and bacteria and skin failed to show that the dye exerted any influence on the course of the inflammation.

Biopsy of stained skin was done in the course of another series of experiments in which the outcome was precisely the same as that presented in table 1. In each instance in which there had been percutaneous bacterial invasion biopsy revealed a typical intracutaneous inflammatory process. From such findings we believe that the presence of blue patches in cutaneous tissues treated with bacteria is a reliable indication of the presence of organisms within those tissues. It appears, therefore, from the experimental data that in a designated shaven area of skin few organisms pass through the already regenerated stratum corneum later than thirty hours after shaving.

TABLE 1.—*Extent of Percutaneous Invasion of Streptococci*

Rabbit No	Amount of Dye Injected 24 Hours Previously, Cc.	Time Broth Culture of Streptococci Was Smeared After Shaving, Hrs.	Degree of Percutaneous Spread*						
			24 Hr.	48 Hr.	72 Hr.	96 Hr.	120 Hr.	144 Hr.	168 Hr.
1	1.5	3	+	++	+++	++++	++++	++++	++++
2	1.5	8	+	+	+++	++++	++++	++++	++++
3	1.5	15	+	+	+	++	++	++	++
4	1.5	24	+	+	+	++	++	++	++
5	1.5	30	±	±	+	+	+	+	+
6	1.5	36	±	±	+	+	+	+	+
7	1.5	48	0	0	0	0	0	0	0
8	1.5	52	0	0	0	0	0	0	0

* + indicates slight extravasation of dye in the tissues; ++, moderate extravasation of dye with noticeable erythema as well; +++, extravasation of dye with erythematous induration, and ++++, extravasation of dye with induration, abscess formation and suppuration.

TABLE 2.—*Extent of Intracutaneous Invasion of Streptococci*

Rabbit No.	Amount of Dye Injected 24 Hours Previously, Cc.	Time of Injection After, Shaving, Hr.	Resultant Lesion 30 Hours After Injection of 1 Cc. of 18 Hr. Broth Culture of Str. haemolyticus (beta) plus*		
			0.5 Cc. Saline Solution	0.5 Cc. Muscle Extract	0.5 Cc. Testicle Extract
1	1.5	4	++	++	++++
2	1.5	10	++	++	++++
3	1.5	15	++	++	++++
4	1.5	24	++	++	++++
5	1.5	48	++	++	++++
6	1.5	72	++	++	++++

* + is used as the unit of extent of the lesion as delimited by the dye.

Influence of Shaving on the Intracutaneous Invasion of Streptococci.—A similar series of rabbits were prepared in the same manner as those used in the previous experiments, except that in this series the streptococci were injected intracutaneously instead of being swabbed on the skin. Tissue factors influencing the intracutaneous spread were likewise added in these investigations. The rabbits were shaved on both sides of the abdomen, and three intracutaneous injections made at the same time of the following bacteria: (1) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of saline solution; (2) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of supernatant fluid of freshly ground muscle; (3) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of supernatant fluid of freshly ground testicle.

The results are presented in table 2.

The lesions which occurred in the foregoing experiment were constant in size under the different conditions present, and the interval after shaving had no apparent effect on the extent of the spread of the bacteria introduced intracutaneously. The average area of staining and induration in those lesions which resulted from the injection of broth culture plus saline solution and broth culture plus muscle extract was 1.5 by 1.5 cm., whereas the lesions produced by the injection of broth culture plus testicle extract was 2.5 by 2.5 cm. Injury to the stratum corneum such as occurs in shaving has no apparent effect on the spread of bacteria when they are placed beneath the superficial layers of the skin; furthermore, agents which augment the intracutaneous spread of organisms, such as the Reynals factor, are not modified by shaving.

COMMENT

The selective nature of many dyes is well known. In this case large molecules of blue azo dye T-1824 remains within the circulatory system only to leave it at foci of increased permeability of a vessel. As we have already indicated, there are certain disadvantages in methods previously used to evaluate the reaction of the skin to foreign bacteria. However, we cannot minimize the importance and the results of Arnold [2] and Colebrook,[1] who succeeded in demonstrating the disappearance of bacteria on the skin by the carefully controlled experiments. We were somewhat unfortunate in attempting to recover organisms in any sort of a quantitative way after the animals had come in contact with their cages. The inevitable contaminations always occurred. Antibody demonstrations and repeated blood cultures are indexes of permeability, but they are too variable to reflect an active process. The method of testing the bactericidal properties of excised skin extracted with alcohol, acetone or ether give interesting results but would seem to lack significance in the face of the evidence that the self-disinfecting power of the skin is a dynamic process with a selective action only on exogenous bacteria. Further observations of Fisher [19] showed that this power varies with the stage of the menstrual cycle, and the investigations of Montgomery [20] demonstrated that it is diminished in diabetes.

The dye method is open to criticism. Mainly it may reflect the passage of toxins or lysates through the skin rather than the presence of bacteria themselves. However, organisms were noted in biopsy preparations, and in those cases in which open abscesses developed streptococci could be easily cultured. The dye in itself exhibits no toxic qualities to the epidermal structures.

Our thesis is that shaving increases the susceptibility of the skin to bacterial penetration, possibly owing to minute abrasions caused by the razor on the keratinized epithelium or to a defense process in the horny layer. It seems reasonable to suggest, on the bulk of evidence

19. Fisher, V.: Proc. Soc. Exper. Biol. & Med. **28**:952, 1931.

20. Montgomery, B. E.: Proc. Soc. Exper. Biol. & Med. **28**:374, 1931.

contributed by other investigators and by our experiments, that shaving before an operation should take place at least thirty hours previous to the incision. This is, of course, with the exception of acute emergencies. It is not denied that after an operation more bacteria penetrate the wound than the surrounding skin, even though freshly shaven, but we suggest that newly shaven skin is more likely to have pathogenic organisms lodged in the cutaneous tissues, and it is through these tissues that the initial incision is made.

CONCLUSIONS

Skin within thirty hours of shaving has an increased permeability to percutaneous bacterial invasion.

Shaving has no effect on the intracutaneous spread of Str. haemolyticus (beta).

An azo dye T-1824 employed intravenously delimits the area of bacterial invasion and inflammation by the blue stain it imparts to infected tissues.

JUXTA-ARTICULAR ADIPOSIS DOLOROSA

ITS SIGNIFICANCE AND RELATION TO DERCUM'S DISEASE AND OSTEO-ARTHRITIS

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Generalized adiposis dolorosa is not common, but it is not easily overlooked on account of the universal distribution of the tenderness of the deposits of fat. Localized hypersensitivity of the fat tissues, on the other hand, is common and often remains unrecognized because it is not looked for or is misinterpreted.

The following report concerns a study of cases of localized tenderness of fat around the joints in 112 patients, who were observed within the last six years.

DEFINITION AND SYMPTOMATOLOGY

I apply the term juxta-articular adiposis dolorosa to accumulations of subcutaneous fat around the joints, which are markedly tender to touch or pressure and are not connected with gross alterations of the sensitivity of the overlying skin. The condition occurs most frequently in obese women past middle age. It is usually bilateral, although one side may be affected more than the other. The distribution is characteristic. Most frequently the tender masses of fat are found at the inner sides of the knee joints. Second in frequence are the inner sides of the elbows. Rarely are the outer sides of the ankles and the hips affected. The tender fat is frequently markedly indurated; in other cases distinct lobules are palpated. Frequently the tender fat is not well defined. In some cases, however, small and larger lipomas are distinctly outlined. In many cases the tenderness spreads from the inner side of the knee over to the anterior aspect of the leg and from the inner side of the elbows to the dorsal aspect of the arm. Symptoms of the menopause and an increase in the systolic blood pressure are present in a high percentage of patients. Of the local symptoms exhibited in the extremities, varicose veins, depressed arches, acroparesthesia and vasomotor disturbances and Heberden nodes are frequently found. The complaints for which consultation is requested consist of stiffness and pain or grating in the joints. Examination reveals in a considerable percentage of cases muscular contraction, limitation of motion, chiefly in the shoulder joints, and some deformity and grating in the knee joint.

From the Orthopaedic Department of the College of Medical Evangelists.

Roentgenograms in some cases show spur formation or osteophytes at the articular surfaces.

On the basis of these symptoms and findings, the diagnosis of osteoarthritis is usually made. The tenderness found during examination is erroneously interpreted as originating from the capsule or the articular surfaces of the joint, while a careful analysis would have revealed that it is due to hypersensitivity of the subcutaneous fat.

APPEARANCE AND METHOD OF EXAMINATION

Inspection in cases of pronounced involvement reveals bulging masses of fat at the inner sides of the knees, the inner sides of the elbows and the external sides of the ankles and the hips. Sometimes an abrupt decrease in the size of the leg below the knee is noted. On the skin frequently thin spider-weblike veins and sometimes large varicosities are present. The sensitivity of the skin to touch, needle pricks and temperature appears to be normal. The response of the minute vessels and capillaries to histamine also is normal. Neither the appearance of the patient nor the inspection of the skin and the masses of fat gives conclusive evidence for a diagnosis of juxta-articular adiposis dolorosa. Systematic palpation is necessary to discover this condition.

A fold of skin and subcutaneous fat is elevated between the thumb and the other fingers, and gentle pressure is applied. It is necessary to be on guard against hypersensitivity of the skin and misunderstanding on the part of the patient. Therefore, the patient's eyes are best covered, and the sensitivity of the skin is tested previously.

Subcutaneous fat in different parts of the body and the joints are examined as a control. Juxta-articular adiposis dolorosa is diagnosed only when there are centers of tenderness in the characteristic areas around the joints, without changes in the more superficial or deeper structures.

ANALYSIS OF MATERIAL

Several hundred persons with juxta-articular adiposis dolorosa were observed during the past six years in arthritis clinics and in private practice in New York and in Los Angeles. In this paper clinical and laboratory data obtained from a study of 112 of these patients are presented and compiled in table form.

The patients complained of stiffness, pain and disability. Objectively they presented few changes in the joints, such as grating on motion and spurs. In only 1 case was acute infectious arthritis present, and in only 3 was there effusion. In no instance was fibrous and osseous ankylosis noted.

No exact data of the incidence of juxta-articular adiposis dolorosa can be given. Symptoms of this condition were found in from 10 to 15 per cent of my patients with osteo-arthritis seen in various clinics in New York and Los Angeles.

SEX AND AGE INCIDENCE

Sex.—Of the several hundred patients with juxta-articular adiposis dolorosa, only 3 were men. The 112 patients used for this study were women. The occurrence of the condition in men, however, may be more frequent than is indicated in my patients with osteo-arthritis, about 80 per cent of whom were women.

Age.—Table 1 gives the distribution of juxta-articular adiposis dolorosa by decades. The youngest patient was 21 years old; the oldest, 71. Only 4 patients (3.58 per cent) were less than 30. There were 15 patients (12.35 per cent) in the fourth decade. In the fifth decade the

TABLE 1.—*Age Incidence*

Ages	No. of Cases	Percentage
21-30	4	3.58
31-40	15	12.35
41-50	40	35.80
51-60	32	30.64
61-70	20	17.90
71	1	0.89
Total	112	

incidence reached its peak, with 40 patients (35.8 per cent), declining in the sixth decade to 32 (30.6 per cent) patients, and in the seventh decade to 20 (17.9 per cent). Nearly two thirds of the patients were therefore between 40 and 60 years of age. About 16 per cent of the patients were under 40 and over 60 years of age. The relation, therefore, to manifestations of the menopause is clearly indicated.

HEIGHT AND WEIGHT RELATIONS

The height of 80 patients is given in table 2. Of these, 28.75 per cent were less than 5 feet (152.4 cm.), 45 per cent were between 5 feet (152.4 cm.) and 5 feet and 2 inches (157.5 cm.) and 23.75 per cent were between 5 feet and 3 inches (160 cm.) and 5 feet and 6 inches (167.6 cm.). Only 1 patient was 5 feet and 10 inches (177.8 cm.) in height.

The weight of 110 patients, clothed but without shoes, was estimated, and the results are in table 3. Only 6.4 per cent of the patients weighed less than 140 pounds (63.5 Kg.); 22.7 per cent weighed between 141 and 160 pounds (64 and 72.6 Kg.), 26.36 per cent between 161 and 180

pounds (73 and 81.6 Kg.), 21.72 per cent between 181 and 200 pounds (82.1 and 90.7 Kg.), 12.6 per cent between 201 and 220 pounds (91.2 and 99.8 Kg.) and 10.8 per cent between 221 and 280 pounds (100.2 and 127 Kg.).

The weight and height relation of 72 patients was compared with the normal values, as compiled in the Medico-Actuarial Mortality Investigation (table 4). Four patients (5.5 per cent) presented values lower than normal. About 10 per cent showed an increase in weight of

TABLE 2.—*Height in Eighty Cases*

Feet and Inches (Cm.)	No. of Cases	Percentage
4 8 (142.2)	2	2.50
4 10 (147.3)	7	8.75
4 11 (149.8)	14	17.50
5 0 (152.4)	20	25.00
5 1 (154.9)	9	11.25
5 2 (157.5)	7	8.75
5 3 (160.0)	5	6.25
5 4 (162.5)	8	10.00
5 5 (165.1)	1	1.25
5 6 (167.6)	5	6.25
5 7 (170.2)	1	1.25
5 10 (177.8)	1	1.25
Total	80	

TABLE 3.—*Weight in Clothes of One Hundred and Ten Patients*

Pounds (Kg.)	No. of Cases	Percentage
111-120 (50.3-54.4)	3	2.72
121-130 (54.9-59.0)	1	0.909
131-140 (59.4-63.5)	3	2.72
141-150 (64.0-68.0)	11	10.00
151-160 (68.5-72.6)	13	11.72
161-170 (73.0-77.1)	11	10.00
171-180 (77.6-81.6)	18	16.36
181-190 (81.6-86.2)	11	10.00
191-200 (86.6-90.7)	13	11.72
201-210 (91.2-95.2)	9	8.17
211-220 (95.7-99.8)	5	4.54
221-230 (100.2-104.3)	7	6.36
231-240 (104.8-108.8)	1	0.909
250-260 (113.4-117.9)	2	1.81
260-270 (117.9-122.5)	1	0.909
270-280 (122.5-127)	1	0.909
Total	110	

less than 20 pounds (9.1 Kg.); about 34 per cent, an increase of between 20 and 40 pounds (9.1 and 18.1 Kg.); over 23.5 per cent, an increase of between 40 and 70 pounds (9.1 and 31.8 Kg.); about 28.5 per cent, an increase of between 70 and 100 pounds (31.8 and 45.4 Kg.), and nearly 3 per cent, an increase of between 120 and 140 pounds (54.4 and 63.5 Kg.). The average increase amounts to about 50 pounds (22.7 Kg.).

BLOOD PRESSURE

The systolic blood pressure was estimated in 50 cases (table 5). In 12 (24 per cent) it was lower than 140 mm. of mercury; in 14 (28 per

cent), between 140 and 150; in 13 (26 per cent), between 150 and 180 and in 11 (22 per cent), between 180 and 220.

Estimation of the systolic blood pressure in relation to age gives an increase over normal average values in 41 cases (82 per cent) and lower values in 9 cases (18 per cent). The average increase in systolic pressure amounted to 23.6 points. In 25 of the 50 cases (50 per cent) the diastolic pressure showed an increase over normal values and in 23 cases (46 per cent) a decrease; in 2 cases (4 per cent) the diastolic

TABLE 4.—*Deviation from the Normal Weight in Seventy-Two Cases* *

Increase in Pounds (Kg.)	Number of Cases	Percentage	Decrease in Pounds (Kg.)	Number of Cases
5- 10 (2.3-4.5)	1	1.47	7 (3.2)	1
10- 19 (4.5-8.6)	6	8.81	10-20 (4.5-9.1)	3
20- 29 (9.1-13.2)	9	13.23		
30- 39 (13.6-17.7)	14	20.59	Total	4
40- 49 (18.1-22.2)	5	7.35		
50- 59 (22.7-26.8)	5	7.35		
60- 69 (27.2-31.3)	6	8.81		
70- 79 (31.8-35.8)	8	11.76		
80- 89 (36.8-40.4)	7	10.30		
90-100 (40.8-45.4)	5	7.35		
120-129 (54.4-58.5)	1	1.47		
130-139 (59-63)	1	1.47		
Total	68			

* The standard of normal weights at different ages and heights is adopted from the report from the Medico-Acturial Mortality Investigation.

TABLE 5.—*Systolic Blood Pressure in Fifty Cases*

Mm. of Hg	No. of Cases	Percentage
100-109	2	4
110-119	2	4
120-129	4	8
130-139	4	8
140-149	14	28
150-159	4	8
160-169	6	12
170-179	3	6
180-189	6	12
190-199	1	2
200-209	2	4
210-220	2	4
Total	50	
Average increase, 23.6 mm. of Hg		

pressure was normal. The average decrease was about 6 points below normal. The diastolic pressure, therefore, showed only a small deviation from the normal.

The pulse pressure showed an increase over normal in 44 cases (88 per cent) and a decrease in 6 cases (12 per cent). The average increase for the series was about 21 points, which is almost identical with the increase in systolic pressures. The increase in blood pressure in these cases, therefore, is characterized by the elevation of the systolic blood pressure in 82 per cent. A marked increase, however (over 180 mm. of mercury), was found in only 18 per cent.

MENSTRUATION AND CHILDBIRTH

Table 6 gives data concerning the menstruation in 89 cases. Twenty-four (27 per cent) of the women still had menstrual periods. Seventeen of these had periods of a normal character, and in 5 (21 per cent) the flow was scanty or irregular. The menstruation was profuse in only 2 (8 per cent). Of the 65 women (73 per cent) in menopause, 17 (26 per cent) ceased menstruating before the age of 40; 12 of these were castrated. Twenty-six (40 per cent) stopped menstruating between 40 and 45 years of age; 4 of these were castrated. Seventeen (26.15 per cent) ceased menstruating between 45 and 50 years of age; 1 of these was castrated. Surgical menopause was induced in 17 women, or about 18 per cent of the total group, or over 26 per cent of those in menopause. Of a smaller group of patients in whom the condition was of recent origin, surgical menopause was induced in about 45 per cent. The frequency of surgical intervention and the fact that about two

TABLE 6.—*Data on Menstruation in Eighty-Nine Cases*

Menopause*	Number of Cases	Percentage	Type of Menstruation	Number of Cases	Percentage
Under 40	17	26.15	Profuse	2	8.33
40-45	26	40.00	Irregular	2	8.33
45-50	17	26.15	Scanty	3	12.50
50-55	1	1.54	Normal	17	70.83
Uncertain	4	6.15			
Total	65		Total	24	

* Surgical menopause was produced in 17 cases (26.15 per cent). Sixty-five (73 per cent) women were in menopause; menstruation was present in 24 cases (27 per cent).

thirds of the patients with juxta-articular adiposis dolorosa were women in menopause emphasize the etiologic significance of the ovarian dysfunction.

Data on childbirth were noted in the histories of 52 patients. Forty-one (79 per cent) of the women were multiparas, 3 (5.8 per cent) had 1 child and 8 (15 per cent) had no children. This prevalence of multiparas was also found among the women with generalized adiposis dolorosa (Dercum's disease).

ONSET OF SUBJECTIVE SYMPTOMS IN THE EXTREMITIES

The development of hypersensitive fat pads, generally not being accompanied by pain, is noticed only by a minority of patients who pay close attention to the shape of their limbs. These occasionally consult a physician for painful "bumps over the joints." As a rule, the presence of the hypersensitive deposits of fat is discovered in the course of consultation for pain, stiffness or grating in the limbs. Table 7 gives the duration of these complaints in 65 patients. In 36 (55.4 per cent), the duration of symptoms amounted to from one to twenty-five years.

In 29 (44.9 per cent) the subjective symptoms were of less than one year's duration. This gives one an opportunity to discover the localized adiposis dolorosa comparatively early. About 94 per cent of the patients were seen by a physician within three years after the onset of symptoms.

DISEASES AND OPERATIONS DURING ADULT LIFE

Eighty-one of the patients gave a history of preceding disease (table 8). Fourteen (17.3 per cent) had diseases referable to, and operations on, the sexual organs. Nine (11.1 per cent) had undergone appendectomy, and cholecystectomy had been performed on an equal number. One patient (1.2 per cent) each suffered from gastric ulcer and cancer of the stomach, respectively. Therefore, 29.6 per cent had diseases of the abdominal organs. In addition, 12 suffered from hemorrhoids (14.7 per cent). Injuries and diseases of the joints unrelated to the present complaints were found in 7 patients (8.6 per cent). Acute infectious

TABLE 7.—*Duration of the Onset of Symptoms in Sixty-Five Cases*

Duration	No. of Cases	Percentage
Less than one year	29	44.6
1-2	10	15.4
2-3	5	7.7
3-4	11	16.7
4-5	1	1.5
5-6	3	4.6
6-10	3	4.6
10-20	3	4.6
Total	65	

polyarthritis was present in 1. A history of phlebitis was given by 4 patients (4.9 per cent), and only 1 patient had suffered from exophthalmic goiter. Three patients gave a history of syphilitic infection. The Wassermann reaction was negative in 2. Mild diabetes was found in 1.

ORAL FOCI OF INFECTION

The condition of the tonsils was noted in 41 patients. Some degree of inflammation was found in 10 (24.4 per cent). The tonsils were normal in 16 (39 per cent), and 5 (12.2 per cent) had undergone tonsillectomy.

The condition of the teeth was noted in 53 patients. Twenty-eight (52.8 per cent) had used plates for years, and 6 had more or less extensive bridge work. Seventeen (32 per cent) had diseased teeth or pyorrhea, and 8 (15.1 per cent) had normal teeth. The percentage of oral infection in this series of patients does not exceed that usually found in persons of the same age and social environment. Therefore, no conclusions as to the relations of oral infection to the development of juxta-articular adiposis dolorosa can be drawn.

ENDOCRINE DISTURBANCES

The majority of the patients showed symptoms of menopause, consisting of hot flushes, headaches, dizziness, nervousness and hypothyroidism, especially thick, dry skin, scanty hair, low basal metabolic rate and characteristic distribution of obesity. In 1 patient this was due to hypothyroidism after thyroidectomy for exophthalmic goiter.

A high degree of endocrine disturbance was found in 10 patients (8.9 per cent). Of these, 4 showed symptoms of pluriglandular disturbances (hypofunction of the ovaries, pituitary and thyroid). One had decalcification of the skeleton, with a calcium content of the blood of 11.8 mg.

TABLE 8.—*Preceding Diseases and Operations During Adult Life* *

Disease and Operation	No. of Cases	Percentage	Comment
Typhoid	2	2.4	
Diphtheria	1	1.2	
Syphilis	3	3.7	Wassermann reaction negative in 2 and positive in 1
Nephritis	1	1.2	
Myocarditis	2	2.4	
Apoplexia	2	2.4	
Eczema	4	4.9	
Psoriasis	1	1.2	
Exophthalmic goiter	1	1.2	Thyroidectomy 10 years previously
Diabetes	1	1.2	
Glaucoma	1	1.2	
Pulmonary tuberculosis	1	1.2	
Gastric ulcer	1	1.2	
Cancer of stomach	1	1.2	
Cholecystectomy	9	11.1	
Appendectomy	9	11.1	
Hysterectomy and ovariectomy	14	17.3	
Phlebitis	4	4.9	
Hemorrhoids	12	14.7	
Facial paralysis	1	1.2	
Herpes zoster	1	1.2	
Injuries to joints	3	3.7	
Other joint diseases	4	4.9	
Sciatica	1	1.2	
Rheumatic fever	1	1.2	
Total	81		

* The data were not complete in a number of cases. Oral foci of infection are discussed separately.

per hundred cubic centimeters, indicating hyperparathyroidism. The basal metabolic rate of 14 patients was estimated; 35.7 per cent showed a minus deviation from normal higher than minus 10. The cholesterol content of the blood of 16 patients was estimated, and 9 (56.2 per cent) presented values over 275 and as high as 375. This marked hypercholesteremia is added evidence of dysfunction of the thyroid glands and is discussed under the laboratory findings. In 6 patients the sella turcica was examined roentgenographically (see table 14); it was found to be normal in 2, large in 2, small in 1 and irregular in 1.

One patient showed calcification of one adrenal gland. The disturbances of the endocrine glands in the majority of patients were not of the type which are associated with hereditary or acquired gross pathologic changes. The largest number of patients were middle-aged

multiparas, and chronic wear and tear of the glands of internal secretions appears to be the significant factor in the production of juxta-articular adiposis dolorosa.

That this symptom complex may, however, develop also on the basis of congenital dysfunction of the endocrine glands is illustrated in the following case.

E. P., aged 19, Jewish, measuring 6 feet (182.8 cm.) in height, weighing 205 pounds (93 Kg.), complained that seven weeks before the present examination, while dancing, he twisted his left leg and collapsed. The knee began to swell, and a contraction developed. He improved under physical therapy, but four weeks later he hit the knee against the dashboard of an automobile. It became more painful, contracted and swollen. He had swelling and locking of the right knee joint. He continued to suffer from attacks of locking in the knee joint and sometimes felt a loose body, which he replaced by manipulation. A diagnosis was made of loose cartilages bilaterally.

The patient had been stout since childhood and suffered from pain and disability of the feet and legs. A diagnosis of a pituitary disturbance was made, and he was given pituitary extracts for several years.

Examination revealed a youth of above normal height and weight, with large extremities and irregular teeth. The left knee was flexed about 120 degrees. It was deformed, but there was no fluctuation at the time of examination. The fat pads at the inner sides of the knee joints were hypersensitive. Roentgenograms made at the age of 13 showed an irregular epiphysis at the metacarpal bones. At the age of 15 the left knee joint showed osteochondritis dissecans at the inner side of the lateral condyle of the femur. In addition to these findings, the roentgenograms showed spurs over the condyles of the tibia; the femur and the articular surfaces of the patella appeared to be highly irregular. The infrapatellar fat pad was very much enlarged.

Laboratory examination showed a sedimentation rate of 7 mm., a hemoglobin content of 90 and 6,200 white cells and 5,025,000 erythrocytes.

The loose body was removed by operation; the enlarged fibrous and inflamed fat pad was resected.

Diagnosis and Résumé.—The patient, a youth of 19 who since childhood had had symptoms of a pituitary disturbance, had juxta-articular adiposis dolorosa. The bones and joints showed spur formation characteristic of osteo-arthritis, usually met only in advanced age.

LABORATORY FINDINGS

In the cases in this series the urine was found to be normal on routine examination, except for the frequent occurrence of traces of albumin. Pus cells and epithelial cells from the bladder and vagina were found in the sediment; in some cases there were also red blood corpuscles. Traces of sugar were found in only 1 case. The examination of the blood for the sugar content in a small number of cases gave results below 100 mg. per hundred cubic centimeters, with the exception of 2 cases in which it was 118 and 140 mg.

The hemoglobin content ranged from a minimum of 62 per cent to a maximum of 100 per cent, with an average of 84 per cent; the blood counts showed erythrocytes (minimum 4,000,000, maximum 6,000,000, average 4,800,000), leukocytes (minimum 5,000, maximum 9,500, average 7,000), polymorphonuclear leukocytes (minimum 36 per cent, maximum 71 per cent, average 58 per cent), lymphocytes (minimum 25 per cent, maximum 60 per cent, average 34.4 per cent) and eosinophilic leukocytes (minimum 1 per cent, maximum 1.5 per cent, average 1.2 per cent).

The blood counts, therefore, did not reveal a conspicuous deviation from normal.

BLOOD SEDIMENTATION RATE

The sedimentation rate of the blood corpuscles was estimated in 50 cases (table 9). The Westergren method was used in 34 and the Linzenmeier method in 16, the values obtained by the latter method being

TABLE 9.—*Blood Sedimentation Rate in Fifty Cases* *

Mm.	No. of Cases	Percentage
1-14	17	34
15-25	14	28
26-40	15	30
41-60	4	8
Total	50	

* In 34 cases, the Westergren method, giving the sedimentation of red corpuscles in millimeters after one hour, was used. In 16 cases the method of Linzenmeier was used, which estimates the time necessary for the corpuscles to sink to a level marked 18 mm. on the special tube. The results then were computed to conform to the values obtained by the Westergren method.

computed to conform with those obtained by the Westergren method. Although 10 mm. is generally given as the high normal value of sedimentation with the Westergren method, in women I consider sedimentation up to 15 mm. in one hour as the limit of the normal on account of the frequency of physiologic processes, especially the menstrual cycle, which tend to elevate the sedimentation rate in normal women.

In only 34 per cent of the cases was the sedimentation rate found to be lower than 15 mm. In 66 per cent the sedimentation rate was increased. In a previous study of the comparative sedimentation rate of blood corpuscles in synovial fluid and blood plasma, I [1] called attention to an increase in the sedimentation rates in a high percentage of cases of osteo-arthritis (over 62.4 per cent). In the presence of effusion the sedimentation rate was increased in fully 82.4 per cent of the cases. In the cases of juxta-articular adiposis dolorosa, which condition is generally confused with osteo-arthritis, there was a prevalence of sedimen-

1. Kling, David H.: Sedimentation Rate of Blood Corpuscles in Synovial Fluid and in Plasma, Arch. Int. Med. **50**:419-434 (Sept.) 1932.

tation values which were higher than normal. The value, therefore, of the sedimentation tests for differentiation between osteo-arthritis and infectious arthritis is limited. The presence of an increased sedimentation rate in localized adiposis dolorosa points either to infectious foci or to an underlying unbalanced equilibrium of the body fluids (a high globulin, fibrinogen or cholesterol content of the plasma).

BASAL METABOLIC RATES

The basal metabolic rate was estimated in 14 cases (table 10). In 8 the values were in the normal range with minus and plus values between 1 and 9. In 3 there was a slight diminution of the basal metabolic rate between 10 and 14 and in 1 a value of plus 12. In only 2 cases (13.3 per cent) was a marked diminution of minus 21 and minus 26, respectively, present. The basal metabolic rate was decreased in only 33 per cent of the cases.

TABLE 10.—*Basal Metabolic Rates in Fourteen Cases*

Deviation	No. of Cases Minus	No. of Cases Plus
0- 9	4	4
10-14	3	1
21	1	0
26	1	0
Total	9	5

BLOOD CALCIUM

The calcium content of the blood was estimated in 15 cases (table 11). In only 1 case was there a marked decrease in the calcium content of 9.2 mg. per hundred cubic centimeters. In 6 cases the calcium values were slightly lower than normal—from 9.6 to 9.9 mg. In 6 cases normal values, between 10 and 10.3 mg., were found. In 1 case the calcium content was 11.1 mg. In this case the roentgenogram did not show a decalcification of the skeleton. In 1 case the calcium content was 11.8 mg., and the roentgenogram showed marked decalcification of the long bones, indicating a possible hyperparathyroidism.

CHOLESTEROL

The cholesterol content of the blood (table 12) was estimated by the modified Bloor method in 16 cases. The normal values in this laboratory are between 160 and 200 mg. per hundred cubic centimeters. In only 2 cases were the values within this range of the normal. In 5 cases (31 per cent) the cholesterol content varied from 200 to 250 mg.;

in 4 cases (25 per cent), from 275 to 300 mg. In 5 cases (31 per cent) there were markedly high values of between 300 and 375 mg.

In the absence of diabetes and nephritis, the elevation of the cholesterol content appears to be due partly to arteriosclerosis and partly to hypofunction of the thyroid. In the majority of cases in which hyperthyroidism was present the cholesterol content was decreased, and in those in which there was hypothyroidism it was increased. The regulating influence of the thyroid on the cholesterol has been established by a number of investigators. Schally [2] found evidence that not only quantitative changes in the function of the thyroid but qualitative changes are expressed in changes of the cholesterol content

TABLE 11.—*Blood Calcium Content in Fifteen Cases*

Mg. per 100 Cc. of Blood	No. of Cases	Percentage
9.2	1	6.6
9.6-9.9	6	39.6
10-10.3	6	39.6
11.1	1	6.6
11.8	1	6.6
Total	15	

TABLE 12.—*Cholesterol Content of the Blood in Sixteen Cases*

Mg. per 100 Cc. of Blood	No. of Cases	Percentage
170-199	2	12.5
200-224	4	25.0
225-249	1	6.2
275-299	4	25.0
300-324	1	6.2
325-350	2	12.5
357-375	2	12.5
Total	16	

of the blood. The latter is therefore a more sensitive indicator of the status of the function of the thyroid than the basal metabolic rate, which indicates only quantitative changes. This is corroborated in this series of cases, in the majority of which there were clinical symptoms of hypothyroidism. The basal metabolic rate, however, was decreased in only 33 per cent, while the cholesterol content of the blood was increased in fully 88 per cent. However, this increase in the cholesterol content was found not only in cases of juxta-articular dolorosa but also in a high percentage of cases of osteo-arthritis. Indeed, I regard abnormally high cholesterol values as the important finding of the blood chemistry in cases of osteo-arthritis.

2. Schally, A. O.: Störung und Regulation des Cholesterinstoffwechsels. Schilddrüse und Cholesterinstoffwechsel, Ztschr. f. klin. Med. **128**:376-386, 1935.

The circulation in the arterioles and capillaries of the skin over the tender fat masses was tested after the method of Starr.[3] The skin was pricked with a needle, and a drop of 1 per cent histamine acid phosphate was applied. The response was normal, as evidenced by development of a wheal and flare within five minutes. In some cases the wheal was reddish instead of the normal white color.

SYMPTOMS IN THE EXTREMITIES AND JOINTS

The subjective symptoms consisted of pain, weakness, stiffness, a feeling of cold and paresthesia in the extremities. They were corroborated by objective findings in 44 cases (39.3 per cent) as follows: rough grating and the formation of spurs, 24 cases (19.5 per cent); increase of infrapatellar fat pad, 12 cases (10.6 per cent); fine grating,

TABLE 13—*Location of Subjective and Objective Symptoms of the Joints* *

Location	No. of Cases	Percentage
Knees	50	44.6
Knees and spine	7	6.2
Knees and hips	3	2.7
Knees and fingers	5	4.4
Knees, ankles and legs	13	11.6
Knees, ankles and arms	4	3.6
Knees, arms and hands	3	2.7
Toes and fingers	4	3.6
Ankles	3	2.7
Hips	9	8.0
Elbows	2	1.8
Wrists	2	1.8
Sternoclavical	1	0.9
Shoulders	3	2.7
Several joints other than knees	3	2.7
Total	112	

* Pain, paresthesia, weakness, swelling, grating or deformity.

5 cases (4.4 per cent), and effusions, 3 cases (2.6 per cent). In the remaining 70 cases (60.7 per cent), no objective findings were present in the joints.

The distribution of both subjective and objective symptoms is given in table 13. In 50 cases (44.6 per cent), the knees alone were involved; the knees and other joints were the seat of the painful deposits of fat in 35 (31.15 per cent). The knees therefore were involved in 85 cases (76 per cent).

DEPRESSED ARCHES AND VARICOSE VEINS

Weak feet were found in 53 cases (56.2 per cent) and varicose veins in 57 (51.7 per cent). In the majority of instances they were not very large. The presence of minute veins which branched off in different

3. Starr, J., Jr.: Change in Reaction of Skin to Histamine as Evidence of Deficient Circulation in Lower Extremities, J. A. M. A. **90**:2092-2094 (June 30) 1928.

directions over the painful deposits of fat was characteristic. The prevalence of depressed arches and varicose veins indicates the type of person who develops juxta-articular adiposis dolorosa. Secondly, it may have indirectly an etiologic relation. The static strain of the weak feet, causing tiredness, leads to insufficient exercise, which increases the body weight and diminishes the circulation in the limbs. This in turn aggravates the varicose veins, thus further impairing circulation and malnutrition of the tissues. Finally, also, the pressure of the deposits of fat impedes the flow of blood. A vicious circle is in this way formed and maintained.

TABLE 14.—*Roentgenographic Picture*

Joints Involved	No. of Cases	Normal	Percentage	Pathologic Picture	
Knees	28	7	25.0	Spurs on the articular surfaces	16
				Hypersensitive fat	2
				Calcified quadriceps tendon	1
				Calcified menisacus	1
				Loose body in knee	1
				Total	21
Shoulders	6	2	33.3	Subacromial bursitis	2
				Calcified acromial spur	1
				Deformed tuberosity of humerus	1
				Total	4
Elbows	1	0	....	Periostitis of epicondyle	1
				Total	1
Fingers	4	1	25.0	Spur at phalangeal joint	2
				Destruction of phalangeal joint	1
				Total	3
Spine	6	2	33.3	Spurs	4
				Total	4
Totals	45	12			
Sella turcica	6	2	33.3	Two large, one small and one irregular	

ROENTGENOGRAPHIC FINDINGS

Roentgenograms of the joints or spine were made in 45 cases in which the clinical findings supported the complaints of the patients and in which hypersensitivity of the fat was marked. The results are presented in table 14.

Of 28 roentgenograms of the knees, 7 (24.6 per cent) were normal. Of the 21 cases in which pathologic changes were pictured, hypertrophic fat pads were visualized by inflation of air into the joints in 2 (17.4 per cent). In 1 case there was calcification of the quadriceps tendon. In only 16 cases was degeneration of the articular surfaces present, as evidenced by spur formation of the patella, tibia or femur. In 1 case loose bodies were found.

The changes of the articular surfaces, therefore, were in the majority of the cases not of a nature that of necessity produces symptoms. In a

large number control roentgenograms of patients past middle age showed identical changes at the articular surface without symptoms of osteoarthritis.

In roentgenograms which showed the soft tissues plain, the enormous increase and cufflike overlapping of the fat masses around the joints were visualized. It was evident that in marked flexion these masses of fat suffer pressure and in consequence give rise to painful sensations (fig. 2).

PATHOLOGIC CHANGES

Biopsy was performed on the hypersensitive fat pads and on overlying skin at the inner side of the knees in 6 cases. Five times small strips of skin and fat about 1 inch (2.5 cm.) in size were removed. In 1 case (see case 1) a large mass of fat was excised from the inner side of the left knee, through an incision about 3 inches (7.6 cm.) long. Grossly the skin appeared normal and the fat was yellowish, and in few cases it was more resisting than normal. The tissues were preserved in formaldehyde and embedded in paraffin. The sections were stained with hematoxylin and eosin and also with special nerve stains made by Dr. Cyrill B. Corville. In all sections the epidermis appeared to be normal. The corium consisted in some sections of loose collagenous fibers and in other sections of denser collagenous fibers. Blood vessels were prominent in some sections, but only few showed sclerotic changes. The fat was of the large vacuole type. In some sections the interlobular fibers were thickened. Several small and large nerves were seen in the fat and corium and appeared to be normal. The minimal changes do not throw a light on the cause of the hypersensitivity of the fat. Interstitial inflammation of the nerves which were found by Dercum [4] and other observers in generalized adiposis dolorosa were not found by the method of examination in the 6 cases in this series. It must, however, be borne in mind that Page [5] and others have found the fat in generalized adiposis dolorosa to be normal histologically and chemically. It is possible that the mere increase of the fat tissue and the accompanying increase in blood supply causes pressure on the nerves and is responsible for the symptoms of hypersensitivity. Increase in the tension of the tissues is evidenced by the frequently found induration of the hypersensitive fat tissues.

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4. Dercum, F. X.: A Case of Subcutaneous Connective Tissue Dystrophy, University M. Mag. **1**:140, 1889; Three Cases of Hitherto Unclassified Affection Resembling in Its Grosser Aspects Obesity, But Associated with Special Nervous Symptoms: Adiposis Dolorosa, Am. J. M. Sc. **104**:521, 1892.

5. Page, Irvine H.: Chemishe Untersuchungen bei der Dercumschen Krankheit, Virchows Arch. f. path. Anat. **279**:262-264, 1930.

LOCALIZATION OF THE HYPERSENSITIVE FAT DEPOSITS

The inner side of the knee alone was found to be hypersensitive in 45 cases (40.2 per cent); in 9 of these (8 per cent) only one knee was hypersensitive (table 15). In the majority of these cases the anterior aspect of the leg over the tibia was also found to be hypersensitive. In 53 cases the inner sides of the knees and the fat pads around other joints were tender (47 per cent). The most common combination was tenderness of the inner sides of the knees and elbows in 29 cases (26.2 per cent); next, the inner sides of the knees and the outer aspects of the ankles in 15 cases (13.4 per cent). The elbows alone were hypersensitive in 1 case, the ankles in 2 and the thighs in 3. Hypersensitiveness of the inner sides of the elbows usually spread to the dorsal aspects of the arms. The knees were involved in 107 cases (95.5 per cent) and should therefore be investigated first, followed by the elbows and the outer sides of the ankles. Indeed, one can predict from the degree of hypersensitivity on the inner sides of the knees the involvement of the other regions. Transition to generalized adiposis dolorosa was found in 3 cases in which the knees and elbows and the outer sides of the thighs were found to be hypersensitive.

TABLE 15.—*Location of Hypersensitive Masses of Fat*

Location	No. of Cases	Percentage
One knee	9	8.0
Both knees	45	40.2
One knee and elbow	4	3.6
Knees and elbows	29	26.2
Knees and gluteal region	2	1.8
Knees, elbows and gluteal region	3	2.7
Knees and ankles	15	13.4
Elbow	1	0.9
Ankles	2	1.8
Gluteal region	2	1.8
Total	112	

THERAPY

All therapeutic measures were usually combined with a reducing diet. They were directed against the complaints and symptoms of the patients as well as against the hypersensitivity of the juxta-articular fat. The modalities of therapy and the results in 70 cases are tabulated in table 16.

In 48 cases (68.6 per cent) no decrease of sensitivity was noticed. In 22 (31.4 per cent) physical therapy was given. It consisted in baking or diathermia, with massage, in 12 cases. There was improvement in only 1 case. Short and ultrashort wave therapy was applied in 3 cases, with decrease of hypersensitivity in 1. In 6 cases histamine cataphoresis was applied to the hypersensitive fat pads. I have described

the technic of this new therapy elsewhere.[6] In 5 cases, a decrease of hypersensitivity was noticed immediately after treatment. However, it persisted for only a short time. Finally, roentgen treatment was given in 3 cases, with improvement in 1.

In 41 cases general measures were applied: Iodine preparations were given in 7 cases and a foreign colloidal iodine preparation for intramuscular injection was given in 6, without effect. In 1 case, iodine and colchicine were injected intravenously, with a decrease in the sensitivity of the fat pads. In 21 cases Crowe's streptococcus vaccine was given subcutaneously, with a decrease in hypersensitivity in 1 case.

Endocrine preparations were used in 30 cases. In 19 ovarian products were administered either by mouth or by injection. In 5 diminution of sensitivity of the fat pads was noted. Thyroid was given in 14 cases. In 3 it had to be discontinued on account of toxic symptoms.

TABLE 16.—*Therapy Employed in Seventy Cases*

Therapy	No. of Cases	Improved	Percentage	Not Improved	Percentage
Baking or diathermia with massage	12	1	8.1	11	91.7
Short and ultrashort wave diathermia	3	1	33.3	2	66.6
Histamine cataphoresis	6	5	83.3	1	16.6
X-ray therapy	3	1	33.3	2	66.6
Injections of saline and procaine hydrochloride solutions	4	1	25.0	3	75.0
Injections of iodine preparation*	6	0	....	6	100.0
Injections of iodine and colchicine	1	1	100.0	0	
Streptococcus vaccine	4	2	50.0	2	50.0
Ovarian preparations	19	5	26.3	14	73.7
Thyroid	11	4	36.3	7	63.6
Excision	1	1	100.0		
Totals	70	22		48	

* An imported colloidal iodine preparation.

Of the remaining 11 cases, ¼ grain (0.016 Gm.) of desiccated glands was given daily in 1 and from 1½ to 3 grains (0.097 to 0.195 Gm.) in the others for a period of from three to sixteen months.

The hypersensitivity of the juxta-articular fat pads was markedly decreased in 4 cases. In 7 the result was entirely negative. In 4 cases 25 cc. of a 0.1 per cent solution of procaine hydrochloride in saline solution gave beneficial results in 1 and negative results in 3. In 1 case, the fat pad at the inner side of the left knee was excised down to the fascia. The hypersensitivity of the fat pad disappeared in the region of the scar, and the fat tissues did not recur. This

6. Kling, David H.: Treatment of Myositis, Arthritis and Disturbances of the Peripheral Circulation with Histamine by Cataphoresis, Arch. Surg. **29**:138-148 (July) 1934; Histamine Therapy of Rheumatic Affections and Disturbances of the Peripheral Circulation, Ann. Surg. **99**:568-576, 1934; Histamine Iontophoresis in Rheumatic and Peripheral Circulatory Disturbances, Arch. Phys. Therapy **16**:466-473, 1935.

result remained permanent up till now for a period of one and a half years' duration (case 1, fig. 1). This result was not duplicated by any of the other modalities. Usual physical therapy measures appeared to be the least effective, while with histamine cataphoresis there was frequently a decrease of hypersensitivity immediately after treatment. The second best result seemed to be in the 4 cases in which there was a reaction to thyroid preparations. However, the reaction fell short of expectations in view of the beneficial results with thyroid preparations reported in Dercum's disease. The excision of the painful fat, which has given such a brilliant result in 1 case, has a drawback of leaving a scar and for this reason cannot be advised as a general procedure.

COMMENT

The nosologic features and the pathologic process of juxta-articular adiposis dolorosa based on a study of 112 cases is presented. From the study it appears that hypersensitive fat pads around the joints prevail in obese multiparas past middle age. The subjective symptoms consist of pain, weakness and acroparesthesia in the extremities. The objective findings point most frequently to a slight or moderate degree of osteoarthritis. The changes in the bony structures, however, were not of such a type necessarily to produce the symptoms. The most frequent roentgenographic findings, the formation of spurs at the articular surfaces, was found in a high percentage of controls of the same age group, who were without symptoms. About 50 per cent had varicose veins, and depressed arches, a moderate or marked degree of hypertension and obstipation were found in a considerable percentage.

In the history of the preceding operations during adult life, castration takes first place, followed by appendectomy and cholecystectomy. Oral foci of infection were not found in excess of what would be expected in persons in the age groups reported on in this series. The majority of the patients showed symptoms of hypofunction of the ovaries and the thyroid gland, and few showed evidence of gross disturbance of the pituitary gland. The endocrine disturbances were more characteristic of chronic exhaustion than of infection or congenital abnormality. The most conspicuous laboratory findings were hypercholesteremia, which was interpreted to be due at least partly to a dysfunction of the thyroid gland. The histologic examination of the hypersensitive fat has, with the methods employed, not revealed any conclusive abnormality.

RELATION OF JUXTA-ARTICULAR ADIPOSIS DOLOROSA TO DERCUM'S DISEASE

Juxta-articular adiposis dolorosa presents the initial and intermediate stages which in rare instances lead to a generalized hypersensitivity of

the fat tissues. In 8 per cent of this series only the fat tissues at the inner side of one knee were hypersensitive, while in 2.7 per cent knees, elbows and thighs appear hypersensitive. With the spreading of the hypersensitivity, the patients showed the physical and mental characteristics of Dercum's disease, namely, debility and lassitude.

The course of Dercum's disease can therefore be mapped out as follows:

The initial stage appears to develop as a single uniarticular hypersensitivity of subcutaneous masses of fat of one knee, the location being mostly the inner side of one knee joint; next the other knee is involved and successively other joints in the lower and upper extremities. Finally, the condition spreads from the extremities to the torso, especially the abdomen and the lateral sides of the chest, the masses of hypersensitive fat on the chest hanging down in large folds.

The endocrine disturbances showed the intermediate stages of those described in Dercum's disease. The hypofunction of the ovaries and of the thyroid and the pituitary gland appears in the majority of cases to be due to exhaustion of the glands of internal secretion rather than to a gross pathologic process. This is also supported by the autopsy observations in cases of Dercum's disease. The thyroid was found to be small and fibrous, with sclerosis, or moderately enlarged with an adenoma. The pituitary gland showed chronic inflammation and sclerotic changes, and in the gonads atrophy and fibrosis were noted.

On the basis of autopsy, observations and clinical signs, Falta[7] rejected the etiology of pluriglandular involvement and insufficiency of different types of lipomatosis which was advanced by Lyon.[8] Falta regarded as the main etiologic factor of Dercum's disease a trophoneurosis due to a dysfunction of the thyroid gland which is related to myxedema.

However, in a smaller number of cases the condition develops on the basis of congenital or acquired diseases of one or more endocrine glands as illustrated in the preceding case history of juxta-articular adiposis dolorosa in a young boy and in cases 6 and 7.

THE RELATION OF JUXTA-ARTICULAR ADIPOSIS DOLOROSA TO OSTEO-ARTHRITIS

The second disease entity which has close relation to juxta-adiposis dolorosa is osteo-arthritis. As was pointed out, pain or disability in the

7. Falta, Wilhelm: Erkrankungen der Blutdrüsen, Berlin, Julius Springer, 1913, p. 477.

8. Lyon, I. P.: Adiposis and Lipomatosis, Arch. Int. Med. **6**:28-120 (July) 1910.

joints was the complaint made by each patient in this series. Only 1 patient had infectious arthritis. The others presented symptoms which were usually classified under osteo-arthritis. Judging by the objective clinical and the roentgenographic picture, the changes in the articular surfaces of the joints were only slight or moderate. In 25 per cent of the cases the roentgenograms of the knee joints were normal, and in 57 per cent spurs of the articular surfaces were noted. These data do not exceed greatly the accidental findings in a group of patients, without symptoms, who belong to a similar age group.

The changes in the articular surfaces have been found frequently to be minimal, even in cases in which the condition is very advanced; therefore, it is justified to assume that the osseous changes are the sequel of soft tissue changes, one of which is presented by juxta-articular adiposis dolorosa.

This is supported by the findings in 11 per cent of the roentgenograms of changes in the soft tissues, consisting of calcification of quadriceps tendon, of hypertrophy of the infrapatellar fat pad and synovial tissue and of periostitis, especially of the anterior aspect of the patella. The frequency of the incidence of obesity, hypertension and arthritis of the knee in women of the climacteric age was emphasized by Gram.[9] While both obesity and hypertension are common around the menopause, he found hypertension and arthritis without obesity in only 4 of 149 patients. On the other hand, obesity and arthritis without hypertension occurred in 16 patients. Obesity, therefore, outranks hypertension by far as a factor in the development of osteo-arthritis. The mechanism by which adiposis dolorosa can produce osteo-arthritis appears to consist of a number of factors.

Circulatory Disturbance.—By diverting the blood supply from the deep structures of the joints (capsule and periosteum), the increased fat masses may produce an insufficient circulation. The pressure on the deep veins obstructs the flow of blood and favors development of varicose veins. These in turn increase the stagnation of the blood. According to Wollenberg, Pemberton and others, circulatory disturbances are responsible for the development of osteo-arthritis.

Mechanical Factors.—The pressure of the increased fat masses on the capsule and periosteum and of the hypertrophic infrapatellar fat pads on the articular surfaces will tend to irritate the joint structures and interfere with the normal motion and thus cause pathologic changes. This is illustrated in figure 2 (case 2), which shows the patella pressed

9. Gram, C. A.: Symptom Triad of the Postclimacteric Period (Adipositas Dolorosa, Arthritis Genu, Hypertensio Arteriolis), Acta med. Scandinav. **73**: 139-207, 1930.

toward the articular surfaces by the cufflike masses of fat. The anterior surfaces of the patella shows periostitis; the insertion of the infrapatellar tendon is calcified.

Functional Disturbances.—Flexion of the joint is most likely to cause pressure on the hypersensitive masses of fat. This in turn causes pain and therefore will be avoided. Interference with the normal function of the joint is the end-result.

REPORT OF CASES

CASE 1 (fig. 1).—A Jewish woman aged 54 complained of pain and stiffness in the knee joints, legs and arms and needle-like pains in the fingers of six years' duration. Her previous complaints consisted of symptoms of dizziness, headaches and cold extremities. Her bowel movements were regular. The menopause occurred at the age of 44. She had sixteen pregnancies. A cystocele and lacerations of the cervix were observed. She suffered from hemorrhoids, pruritus and eczema.

She weighed 185 pounds (83.9 Kg.) and was 57 inches (144.7 cm.) tall. Obesity was especially prominent over the buttocks, thighs and abdomen. The extremities were short. The hair was scanty under the axilla and on the mons veneris. There was a marked growth of a mustache, and the features were coarse. The lower teeth were extracted, and the patient used an upper plate. The veins were moderately varicose. The blood pressure was 130 systolic and 90 diastolic. The lungs, chest and heart were normal, as were the pupillary reflexes and ocular fundi.

The urine contained traces of albumin and epithelial cells from the bladder and vagina. The Wassermann reaction was negative, and the basal metabolic rate, minus 1. The cholesterol content was 362 mg. per hundred cubic centimeters; the calcium content, 10 mg. and creatine content, 4.3 mg.

Heberden nodes were present over the second phalangeal joints. There was no fluctuation or limitation of motion in the other joints. The masses of fat over the inner aspect of the knee joint and of the tibia were hard and sensitive to touch. Also the fat over the inner sides of the elbows and the dorsa of the arms was hypersensitive. A roentgenogram of the right knee joint was normal. A roentgenogram of the spine showed bridging at the third, fourth and fifth cervical vertebrae.

The patient was given a reducing diet of 800 calories and 3 grains of desiccated thyroid daily. In the course of two years, she received intravenous injections of typhoid, ultraviolet therapy, histamine cataphoresis and injections into the varicose veins without reduction of hypersensitivity of the fat pads. In March 1934 the fat on the inner side of the left knee was excised up to the fascia. The wound healed without complications. Histologic examination of the fat did not show any abnormality. The hypersensitivity disappeared in the region of the scar (fig. 1) and did not recur for the period of one and one-half years.

The diagnosis was multiple juxta-articular adiposis dolorosa with evidence of hypo-ovarian and hypothyroid obesity. The roentgenogram of the knee joint was normal. This is the only case in which permanent cure was achieved by excision of the hypersensitive fat at the left knee joint. One and a half years of thyroid medication did not have any effect on the other juxta-articular hyper-

sensitive masses of fat. On the contrary, the hypersensitivity progressed to the masses of fat at the lateral side of the chest, the abdomen and the back, increasing muscular weakness and mental instability. The patient now offers a full-blown picture of Dercum's disease.

CASE 2 (fig. 2).—A Jewish woman aged 45 complained of pain in the shoulders and chest. The pain in the legs was of fourteen years' duration. She had typhoid at the age of 13, and one year before the present trouble varicose veins had been obliterated by injections. Tonsillectomy was performed at the age of 28. The patient suffered from arthritis of the knees fourteen years before the present illness and spent four weeks in a plaster of paris cast. She had four children, and her menstruation was regular, the periods being of four days' duration. She was 5 feet and 4 inches (162.5 cm.) in height and weighed 270 pounds (122.5 Kg.).

Examination showed obesity, especially at the buttocks, abdomen and inner sides of the knees. Some individual knots of fat were present in these places. Over the knee joints, the fat formed cuffs, and the inner sides of the knees were tender to touch. The teeth showed pyorrhea. The blood pressure was 140 sys-

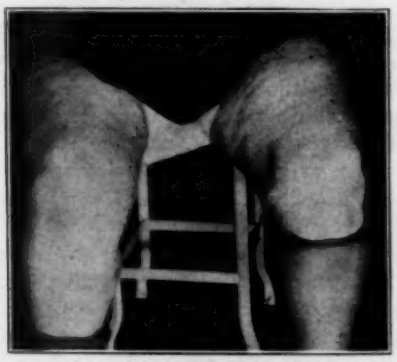

Fig. 1 (case 1).—Advanced juxta-articular adiposis dolorosa (transitional stage of generalized adiposis dolorosa). Bulging masses of fat are present over the inner side of the right knee. On the left knee there is a scar 3 inches long from excision of fat. Note the depression in the region of the scar.

tolic and 100 diastolic. The heart and chest appeared to be normal. There was tenderness over the shoulder and cervical portion of the spine. The urine was normal, and the sedimentation rate was 17 mm. per hour. The patient appeared to be of average intelligence.

On roentgen examination the spine was found to have small spurs at the upper and lower margins of the dorsal and lumbar vertebrae. The shoulders were normal, and the bone structure of the knees (fig. 2) was hazy. There was an enormous amount of fat over the joint line, forming folds which extended about 2 inches (5 cm.) below the head of the tibia. The patella was pressed toward the femur. There was periostitis over the anterior aspect at the insertion of the infrapatellar tendon.

A reducing diet and Crowe's streptococcus vaccine were given, with no effect on the hypersensitivity. This case of multiple juxta-articular adiposis dolorosa (fig. 2) illustrates the pathologic changes produced by the hypersensitive masses of fat over the knee joints.

CASE 3 (fig. 3).—A Jewish woman 58 years of age, measuring 5 feet and 3 inches (160 cm), weighing 225 pounds (102 Kg.), compained of pain in the legs of several years' duration, which was especially severe on walking. She had previously suffered from bronchitis and constipation. The menopause took place at 48. She had seven children.

On examination (fig. 3) it was found that she was obese, especially in the lower half of the body. The arches were depressed, and the fat pads at the inner sides of the knees were hypersensitive. Below the knees a constriction was seen which corresponded to the pressure of garters. The fat formed folds over the ankles. The fat over the upper extremities and the chest was not increased and had normal sensitivity.

Fig. 2 (case 2).—Lateral roentgenogram showing juxta-articular adiposis dolorosa of both knees. Enormous cufflike masses of fat are present over the knee joint. Note the approximation of the patella to the femur and calcified periostitis over the lower and anterior part of the patella at the insertion of the infrapatellar tendon.

Injections of an ovarian preparation were given with no result. The diagnosis was juxta-articular adiposis dolorosa at the inner sides of the knees, with distribution of obesity characteristic for hypofunction of the thyroid gland and ovaries. The constriction under the knees was due to circular garters. It was frequently encountered in these cases and may be a contributing factor to the prevalence and early onset of the condition around the knees.

Case 4 (fig. 4).—A Jewish woman aged 43 complained that several weeks before the present examination she noticed a swelling over the right hip, which was painful, especially on bending forward. She had influenza in 1918 and hemorrhoids and frequent colds. She had seven children. Menstruation was starting to diminish. She was 5 feet, 4 inches (162.5 cm.) tall and weighed 150 pounds (68 Kg.). She was nervous and mentally unstable. No history of venereal disease was obtained.

Examination showed her features to be coarse; the neck was small, and the thyroid was not palpable. The arches showed a slight degree of weakness. There was no general obesity, but there was a mass of fat over the right hip joint, which was tender to touch, and the inner side of each knee and that of the right elbow were tender.

Fig. 3 (case 3).—Juxta-articular adiposis dolorosa of both knee joints. Note the distribution of fat over the lower part of the body, the constriction of the garters under the knees and the bulging fat at the knees and ankles.

The sugar content of the blood was 118 mm. and the hemoglobin content, 75 per cent. The red cells numbered 4,768,000; the leukocytes, 8,500; the segmented neutrophils, 50; the nonsegmented neutrophils, 1; the lymphocytes, 44; the eosinophils, 1, and abnormal cells, 4. The basal metabolic rate was 12 plus, and the Wassermann reaction, 4 plus. The urine was normal on repeated examinations. Roentgen examination showed the ankles and shoulders to be normal, and a small spur present on the right knee.

This is a case of multiple juxta-articular adiposis dolorosa in an early stage in an otherwise not obese patient. The appearance of a hypersensitive mass over the right hip was noticed by the patient for only a few weeks. She had tertiary syphilis.

Case 5.—A Jewish woman aged 53, weighing 183½ pounds (83.2 Kg.) and measuring 57¾ inches (146.7 cm.) in height, complained of a pain in the right

side of the hip and for the past three years of a pain in the lumbar region. In her youth she had suffered from headaches. Previous complaints included coughing and choking, and she had a renal condition, which was diagnosed as nephroptosis. She had eczema at the ears, rhinitis and scoliosis of the dorsal and the lumbar portion of the spine, which was treated by wearing a corset. Tonsillectomy had been performed four years before the present illness. She had had false teeth since 12 years of age. The menopause took place at 42. She had been obese since youth, and her intelligence was normal.

Examination showed obesity, especially over the buttocks, abdomen (apron-like) and thighs and the inner side of each knee, but only slight hypersensitivity. There was a marked hypersensitivity over the inner side of each knee and of each elbow. The thyroid was not palpable. There was no hair under the armpits, and the patient stated that she had never had hair there. There was scanty hair over the eyebrows and in the pubic region. The veins were moderately varicose. The heart and chest were normal.

Fig. 4 (case 4).—Incipient juxta-articular adiposis dolorosa. Note the bulging masses of fat over the right hip.

Roentgen examination showed that there was scoliosis of the dorsal portion of the spine, with convexity to the right and a slight degree of coxa vara of the right femur. The urine was normal, and the Wassermann reaction was negative. The calcium content of the blood was 9.8 mg. per hundred cubic centimeters and the cholesterol content, 284 mg.

The patient was put on a reducing diet, and 3 grains of thyroid daily was given for four months. The patient lost 22 pounds (10 Kg.), but the hypersensitivity was not influenced and was spreading.

This case of multiple juxta-articular adiposis dolorosa illustrates the failure of thyroid therapy to reduce the hypersensitive fat, although a marked reduction in general weight was noticed.

Case 6.—A white woman aged 47 complained of pain in both arms, shoulders and knees of two years' duration. She also complained of heart burns and pain in the epigastrium. She had undergone panhysterectomy fifteen years before the

onset of the present condition, and after that there was an increase in obesity. Cholecystotomy was performed thirteen years before, and she suffered from constipation. Her oral hygiene was poor, and she had used false lower teeth for one and one-half years—two bridges—and a partial upper plate.

Examination showed her features to be coarse. She had a large nose, which she stated had grown larger since last year. The extremities, especially the hands, were large. The breasts were pendulous, and she had dry skin, although the hair was normal. She had marked knock-knees, especially of the right leg. The skin blanched after exposure to cold water for several minutes. The eyelids were puffy. There was a doughy swelling over the first phalanges of both hands. The right knee joint was 2 inches larger than the left. Fluctuation was present. A viscid turbid fluid (10 cc.) was aspirated which contained rice bodies. There were masses of fat the size of an orange on the sides of the knees, which were tender, and also there was a tenderness at the inner sides of the elbows and at the hips over the abdomen. The arms could be elevated only to 110 degrees. There was weakness in the gripping of the hands and tenderness over the third and fourth lumbar vertebrae. The blood pressure was 170 diastolic and 100 systolic. The patient had three children.

The urine showed traces of albumin and occasional hyaline casts. The blood contained 4,400,000 red cells, which under treatment increased to 5,600,000, and 80 per cent hemoglobin, which increased to 93 per cent. Under treatment the leukocytes increased from 6,600 to 9,500; the neutrophils from 35 to 50 per cent, respectively, while the lymphocytes decreased from 60 to 45 per cent, respectively.

Roentgen examination showed lipping and spurs at the articular surface of the right tibia and femur and a large sella turcica. The floor was smooth, but the posterior clinoid processes appear to be irregular. The right shoulder showed a spur at the acromioclavicular joint.

After aspiration of the fluid from the right knee, there was no recurrence of the fluid. Mild fever therapy in an infra-red cabinet and 3 grains of desiccated thyroid were given daily for a period of one and a half months. The patient lost 17 pounds (7.7 Kg.), and palpitation of the heart developed. The daily dose of thyroid was discontinued, and she regained 3 pounds (1.3 Kg.) in one week.

This case shows a transition of the juxta-articular adiposis dolorosa to generalized adiposis dolorosa. Clinical and roentgen tests showed evidence of pituitary disease and possibly the beginning of acromegaly, with physical debility and mental dulness. The patient was one of the two patients in this series who had effusion in the knee joint.

Case 7.—A Jewish woman aged 48 complained of pain radiating from the neck to the right arm and shoulder and of stiffness of the right knee, which was especially noticeable after sitting. She also complained of frontal headaches and numbness in the fingers.

She had had a fibroid tumor of the uterus, for which she received irradiation four years before the onset of the present illness. Hemorrhages had occasionally been present in the uterus, which was treated with injections of theelin for eight months. She had eight children, and was 4 feet and 9 inches (144.7 cm.) tall and weighed 172 pounds (78 Kg.).

Examination showed scanty eyebrows and a small neck; the thyroid was not palpable. The feet and hands were small, and there were masses of fat around the abdomen and thighs. The inner sides of the knees and of the elbows were

hypersensitive. The blood pressure was 160 systolic and 84 diastolic. The lungs and heart appeared to be normal. The tonsils appeared to be chronically inflamed. The patient was dull intellectually and emotionally unstable.

On laboratory examination the hemoglobin content was found to be 82 per cent. The leukocytes numbered 8,600. The calcium content of the blood was 10.1 mg. per hundred cubic centimeters and the cholesterol content, 301 mg. The basal metabolic rate was minus 14. A roentgenogram showed the cervical portion of the spine to be normal and the sella turcica very small.

Biopsy was done of a strip of skin and subcutaneous fat of the inner side of the left knee, which was grossly and histologically normal. After the biopsy there was profuse uterine bleeding for ten days. One and a half grains of desiccated thyroid was given, which was discontinued on account of dizziness.

The diagnosis was multiple juxta-articular adiposis dolorosa in a patient suffering from the menopause syndrome. Dysfunction of the ovaries and of the thyroid gland, with a gross pathologic process of the pituitary gland, was also suggested by the small sella turcica.

Case 8.—A Jewish woman aged 62, weighing 182 pounds (82.6 Kg.) and measuring 58¾ inches in height (149.2 cm.), complained that for the past two years she had had a cramplike pain in the left leg with dizziness, and for the past several months there was pain in the right knee. The patient also noticed a tenderness at the inner side of the right knee. The blood pressure was 230 systolic and 120 diastolic.

The patient had neuritis eleven years before the present illness; herniotomy and hysterectomy for a fibroid tumor of the uterus had been performed five years before and tonsillectomy three years before; the patient also had glaucoma simplex of the right eye.

On examination the obesity was found to be especially prominent over the abdomen, buttocks and thighs. The pupillary reflexes were normal, and the thyroid gland was not enlarged. The lungs were normal, and there was an enlargement of the heart to the left. The second aortic sounds were accentuated. The right knee joint was swollen and fluctuating. There was marked tenderness of the inner side of each knee and over the quadriceps tendon. The veins were slightly varicose. The motion of the knee was normal. A roentgenogram showed a small spur at the medial side of the articular surface of the tibia and the femur. The right hip joint was not changed, with the exception of osteoporosis of the head of the femur, which appeared in some places in the shape of round areas of decalcification. This was perhaps due to cystlike mucinous degeneration. The ocular fundi and visual fields were normal.

The urine showed traces of albumin, some pus and blood and epithelial cells of the bladder and vagina. The basal metabolic rate was plus 7. The cholesterol content of the blood was 262 mg. per hundred cubic centimeters, and the sugar content, 114 mg.

Biopsy of a strip of skin and fat 1 inch long at the inner side of the knee showed the corium to consist of coarse hyaline fibers. A large normal nerve trunk was seen. The fat was normal, with the exception of the increase in interlobular and collagenous fibers.

Twenty cubic centimeters of straw-colored viscid fluid containing fibrinous threads was aspirated. There were 400 cells per hundred cubic centimeters, and cultures in Rosenow's medium were negative. After aspiration, eighteen short wave diathermia treatments and finally six histamine cataphoreses were given. The fluid did not recur, and the tenderness over the quadriceps tendon disappeared.

The patient took 3 and 2 grains of desiccated thyroid (2.7 Kg.), respectively, for three months and lost 6 pounds. There was no effect on the tenderness over the fat masses.

A diagnosis of bilateral juxta-articular adiposis dolorosa of the knee joints with effusion in the right knee joint was made. There was a history of profuse menstruation. Hypertension and dysfunction of the thyroid and of the ovaries were noted. Although the symptoms referable to the joints were of three years' duration, the roentgenogram showed no marked changes, and the treatment promptly relieved the effusion and swelling of the joint proper. However, neither physical therapy nor thyroid medication had any effect on the tenderness of the masses of fat at the inner side of the knee.

Case 9.—A Jewish woman aged 38, measuring 5 feet (152.4 cm.) in height and weighing 104 pounds (47.2 Kg.), complained of neuralgia on the right side for one year, with pain in the elbows and the finger joints of the right hand. Her hands and feet were stiff in the morning, and she suffered from headaches.

Her previous diseases included inflammatory rheumatism at the age of 13, chorea for three years, and vomiting for eight weeks at the age of 24. She had had extreme protrusion of the eyes and weakness of the heart. Exophthalmic goiter due to a substernal goiter was diagnosed, and ligation of the vessels of the thyroid was performed. Two years later a diagnosis was made of ulcer of the stomach, and the patient was put on a strict diet. An abscess of the pelvis was drained through the vagina, and three years before the present illness hemorrhoidectomy was performed. She suffered from chronic constipation. Her menstruation, which was profuse, lasted from seven to eight days, with an interval of fourteen days between periods. There was no pregnancy.

The family history showed that the patient's mother had scoliosis and myocarditis and an uncle had infectious polyarthritis.

On examination the patient appeared to be markedly nervous. The lungs were normal, and the heart sounds were muffled, but there was no evidence of valvular disease. The eyelids were puffy; there were an abundance of hair and a moist skin. The fat increased around the abdomen and buttocks. The blood pressure was 90 diastolic and 85 systolic. Configuration and motion of the joint were normal, and the hands and feet were cyanotic, cool and clammy. There was a contraction of the anterior metatarsal arches. The fat pad at the inner side of the left knee was tender. The urine was normal, and the blood sedimentation rate, 4 mm.

Correction of posture and change in habits relieved the constipation. The vasocirculatory and joint symptoms were treated for seven months by physical therapy and the administration of ovarian preparations, an estrogenic preparation and a follicle-stimulating principle in conjunction with 1½ grains of thyroid daily. One course of injections of chaulmoogra oil was given. Only temporary relief was derived from all these measures. The menstruation was not influenced, nor was any appreciable rise in the blood pressure noticed. During this time the patient had several attacks of swelling and effusion of the knee of one or two days' duration. One of these attacks followed alcoholic abuse. She claimed that she had a retention of the urine for a day simultaneously with the attack.

The diagnosis was juxta-articular adiposis dolorosa of the left knee joint in a patient showing marked dysfunction of the thyroid gland and ovaries with symptoms of a transition of hyperthyroidism associated with exophthalmic goiter into hypothyroidism after thyroidectomy was performed. Deficiency of the peripheral

circulation, transitory edema, effusion into the joint, retention of urine and marked hypotension seem to indicate incipient myxedema. The juxta-adiposis dolorosa is at present confined to one knee.

CASE 10.—A woman aged 43 complained of a pain in the right arm and in the back, of two years' duration. Previously there was a pain also in the left side. She was 59½ inches (151 cm.) tall and weighed 157 pounds (71.2 Kg.). Surgical menopause took place at 35. She had two children.

Thirteen years before the present complaint she had influenza and eleven years before, tuberculosis of the lung, which was treated for six months in a sanatorium. One son died of tuberculosis. Tonsillectomy was performed fifteen years before and hysterectomy was done at the age of 35. One year before this consultation she was treated for hot flushes with injections of theelin. Two years before a tumor was removed from under the knee and left shoulder (lipoma?). The gallbladder was drained six years before, and hemorrhoidectomy was performed one year before. The patient suffered from constipation.

Examination showed the patient to be normally developed, with no enlargement of the thyroid. She also had kyphosis of the dorsal portion of the spine and cyanosis of the face and extremities. The heart appeared to be normal, as did the electrocardiogram. Percussion revealed dulness over the apexes, and there were small hard axillary and supraclavicular glands. The fingers showed Heberden nodes. There was no disfiguration of the right shoulder, but motion was limited to 120 degrees of elevation. The right pupil was larger than the left, though both reacted promptly to light and in accommodation.

Roentgenographic examination of the chest showed increased hilus and peribronchial thickening and infiltration of the infraclavicular region, with numerous small calcifications in the lung. A roentgenogram of the kidneys showed a calcified spot at the upper pole, which was movable with the right kidney and was interpreted as a calcification in the right adrenal gland. A roentgenogram of the shoulder was normal and one of the dorsal portion of the spine showed spur formation.

Laboratory examinations showed the urine to contain albumin and sometimes pus cells. The sedimentation rate of the blood was 14 mm. The basal metabolic rate was minus 2; the calcium content of the blood, 9.2 mg. per hundred cubic centimeters; the cholesterol content, 220 mg. and the nonprotein nitrogen, 22 mg. The tuberculin tests were positive with tuberculin in dilutions up to 1:1,000,000.

Biopsy of a strip of skin and fat from the inner side of the right knee did not reveal any abnormality on histologic examination.

The patient was given one injection of tuberculin weekly for eight weeks, and the pain in the right arm subsided for five months. After recurrence, treatment was continued. She received 1½ grains of thyroid daily for a month and lost 6 pounds (2.7 Kg.). No influence on the tenderness of the fat pads was noticed. The patient was transferred to a relief agency.

A diagnosis of multiple juxta-articular adiposis dolorosa was made. The climacterium was induced surgically. The history and the roentgenogram showed evidence of fibrous tuberculosis of the lungs, with a pronounced tendency to calcification. Calcification of the right adrenal gland was also visualized in the roentgenogram. The administration of thyroid had no effect on the hypersensitivity of the fat.

CASE 11.—A white woman aged 60, measuring 5 feet and 6 inches (167.6 cm.) in height and weighing 180 pounds (81.6 Kg.), complained of pain in the knees for two months. Six years before the present complaint she had thrombophlebitis

of the right leg; cholecystectomy was performed one year later. She had received roentgen irradiation for uterine hemorrhages, and since then menstruation had ceased. Her bowel movements were regular. She had four children. Her teeth were extracted.

Examination showed general obesity, varicose veins and depressed arches. The infrapatellar fat pads were increased in the knee joints, and the masses of fat at the inner sides of the knees were hypersensitive. A roentgenogram made with inflation of air showed masses of fat pressing cufflike around the knee joint, evidently pushing the patella toward the femur. The internal fat pads were markedly increased. The patient received histamine cataphoresis with indefinite effect on the hypersensitive fat.

A diagnosis of juxta-articular adiposis dolorosa at the inner sides of the knee joints was made. The hypertrophic fat pads within the joints in addition to the subcutaneous fat masses around the joints were visualized roentgenographically with inflation of air. No effect of histamine cataphoresis was noticed on the hypersensitivity of the fat.

Case 12.—A white woman aged 58 complained of swelling and stiffness of the right knee and pain of the left arm. She suffered from hot flushes, dizziness, palpitation and constipation. Surgical menopause took place at 41. She had four children. Hysterectomy and appendectomy were performed at the age of 41.

Examination showed the patient to be nervous. No general obesity was noted. The blood pressure was 210 systolic and 110 diastolic. The heart was enlarged, and there were varicose veins. The knee joints, especially the right, showed hypersensitive masses of fat at the inner and the lateral sides of the ankle joints.

A roentgenogram of the right knee showed only calcification of the insertion of the quadriceps tendon at the patella. The urine was normal, and the Wassermann reaction was negative.

Injections of iodine and ovarian preparations were given, and the pain in the right arm and right knee decreased. There was no effect on the hypersensitivity. For this reason, a series of roentgen treatments was given, after which the sensitivity disappeared over the inner side of the knee. Procaine hydrochloride and alcohol were injected into the sensitive masses of fat at the inner sides of the ankles, and the tenderness disappeared. However, the follow-up period was short, and the duration of the therapeutic effect is uncertain.

A diagnosis of juxta-articular adiposis at the knees and ankles was made in association with a climacterium induced surgically. There was no obesity but marked hypertension. Roentgen treatment relieved the hypersensitivity at the inner sides of the knees. Injections of procaine hydrochloride had a good effect on the hypersensitive fat of the ankles.

Case 13.—A Jewish woman aged 52 complained of pain in the feet, knees and right shoulder of three years' duration. For three months she noticed a swelling of the inner sides of the knees. The menopause was starting. The patient had five children. Her intelligence had decreased.

Examination showed a pale small neck, obesity, which was especially pronounced at the abdomen, and dermographism. There were no previous diseases or operations. The patient had used false teeth for three years. She had enlarged tonsils and varicose veins. At the inner sides of the knees there were tender masses of fat of the size of a small apple, which were more indurated and less movable than the skin at the other side. On the inner sides of the elbows tender masses of fat the size of a walnut were present.

Baking and massage increased the pain. Injections of iodine were given.

A diagnosis of juxta-articular adiposis dolorosa in the knees and elbows was made. The tender masses of fat were increased and formed larger and smaller nodes. The patient noticed the enlargement of the masses.

CASE 14.—A Jewish woman aged 53 complained of pain in the feet and legs for two years. Examination showed weak feet and varicose veins. She had used false teeth for ten years. The menopause took place at the age of 43. She had seven children. The sedimentation rate was 13 mm.

A roentgenogram of the region of the left knee showed a spur of the tibia and the femur. The patella was pressed toward the femur and showed a separate fragment (broken spur at the upper pole).

Baking and massage increased the pain. Arch supports were worn, and injections of an ovarian preparation were given. The pain and the tenderness decreased for several months.

A diagnosis of multiple juxta-articular adiposis dolorosa was made. Temporary improvement was noted after the ovarian therapy.

CASE 15.—A Jewish woman aged 44 complained of a pain in the left knee of three weeks' duration. She was still menstruating and was the mother of eight children. Her bowel movements were regular.

Examination showed general obesity. The blood pressure was 150 systolic and 85 diastolic. She had small feet and hands, which were cyanotic and felt numb. She had a small neck. The thyroid gland was not palpable. The arches were depressed, and the veins were moderately varicose. Masses of fat the size of a walnut protruded at the inner side of both knees and were sensitive to touch. The infrapatellar fat pads were markedly large but not sensitive. The painless right knee showed more marked grating on motion than the left knee. There was limitation of flexion in the left knee to about 50 degrees on account of pain.

A roentgenogram of the left knee showed only a slight irregularity of the patella. The fat was enlarged. Histamine cataphoresis was given six times, and the range of motion increased to 90 degrees of flexion. The hypersensitivity of the fat pad diminished, but temporarily.

The diagnosis was juxta-articular adiposis dolorosa of the knees, with decrease in flexion on account of pain. Histamine cataphoresis diminished hypersensitivity and increased the range of motion.

SUMMARY

A study of 112 cases of hypersensitive masses of fat at the joints is presented.

The term juxta-articular adiposis dolorosa is suggested for this condition, to express the location and the relation to generalized adiposis dolorosa.

The condition prevails in obese multiparas past middle age.

The condition is frequently associated with hypertension, varicose veins and depressed arches.

Subjective symptoms consist of pain, weakness, stiffness in the joints, acroparesthesia and circulatory disturbance in the extremities.

The inner sides of the knees were involved in 95 per cent of the cases. In 8 per cent only one knee joint was hypersensitive. In all others the condition was bilateral.

Clinical and laboratory examination revealed in about 60 per cent of the cases slight or moderate osteo-arthritis; in 11 per cent, soft tissue changes, such as hypertrophy of the infrapatellar fat pads, and periostitis, especially over the patella or calcification of the insertions of quadriceps tendon, were noted. Joint effusions were present in 2.6 per cent.

Among diseases and operations in the adult life of patients, castration, appendectomy and cholecystectomy were conspicuous.

Oral foci of infection were not found in excess of what would be expected in patients of the age groups in this series.

Hypofunction of the ovaries and of the thyroid and the pituitary gland was frequently found. In the majority of cases glandular disturbances were characteristic of chronic exhaustion rather than of acquired or congenital gross pathologic processes.

The basal metabolic rate was lower in only 33 per cent. In 87 per cent a definite hypercholesteremia was found, which appeared to be partly due to dysfunction of the thyroid.

Biopsies of fat pads did not reveal definite pathologic processes.

Juxta-articular adiposis dolorosa is regarded as the initial and intermediate stage of generalized adiposis dolorosa.

Juxta-articular adiposis dolorosa is recognized as one of the soft tissue changes which leads to the development of osteo-arthritis by interference with the blood supply, by pressure and irritation of the structures of the joint and by interference with the function of the joint.

Permanent disappearance of hypersensitivity and reduction of the fat followed excision in 1 case. All other therapeutic measures, including the administration of thyroid and ovarian preparations, histamine cataphoresis and roentgen therapy, had only a partial and frequently transitory effect on the hypersensitivity of the fat pads.

Dr. Cyrill B. Corville, of Los Angeles, supplied special stains of the biopsy sections, and Dr. David Saschin, of New York, furnished some of the follow-up data.

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TREATMENT OF BRAIN ABSCESS ASSOCIATED WITH EXTRACAPSULAR NECROSIS AND SUPPURATION

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The experience gained in the treatment of two patients with abscess of the brain associated with extracapsular necrosis and suppuration forms the basis of this paper. These are the only patients with this type of abscess whom I have ever seen. Both were operated on, and both recovered. In presenting this subject with the report of the cases, I hope that the information obtained from the observations made will be of help to others in dealing with similar cases.

In reviewing the literature one does not find reports of many cases of nonoperative abscess of the brain in which definite pericapsular or extracapsular involvement in the nature of necrosis and suppuration was present. This may be due to the fact that autopsy was not performed or that the condition found at autopsy was not completely described. Probably Macewen [1] and Eagleton [2] have given more attention than most writers to the detailed description of the individual cases observed by them. In one instance Macewen (case 28) stated that "it was evident that there was a considerable zone of purulent inflammation surrounding the abscess cavity," but this was only an assumption, as the area was not completely inspected and observed. The patient recovered. In another instance (case 30) Macewen removed at autopsy a rather large capsule which was completely floating in pus. The abscess ruptured into the ventricle. In other instances he spoke of the abscess cavity's being "surrounded by a slightly reddish-yellow zone," or "red softening of the brain."

Eagleton reported a case (case 9) in which the pathologic process was similar to that in the two cases here reported. He also gave his reasons for the formation of secondary abscesses as follows: "encephalitis induced in surrounding tissue by the trauma of exploration or evacuation" and "encephalitis by direct extension from the primary

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Read before the Section of Neurology and Psychiatry of the New York Academy of Medicine, April 9, 1935, and before Westchester Surgical Society, April 23, 1935.

1. Macewen, William: Pyogenic Infective Diseases of the Brain and Spinal Cord, Glasgow, J. Maclehose & Sons, 1893.

2. Eagleton, W. P.: Brain Abscess: Its Surgical Pathology and Operative Technic, New York, The Macmillan Company, 1922.

abscess, the path of infection, though frequently small, being discoverable by careful examination." In the large number of cases reviewed by him there probably were a number similar to the two reported here.

Mosher [3] removed a capsule in its entirety. Bagley [4] also reported a case in which the same procedure was carried out. Adson and Craig [5] reported the removal of an encapsulated abscess without being aware of its nature until the mass was opened. The wound healed by primary intention without drainage. Evidently extracapsular suppuration or necrosis was not present. Cahill,[6] in a report on his series of cases of abscess of the brain, in which the recovery rate was high, did not mention extracapsular involvement. In 1930 Coleman [7] stated that in his experience death after operation in all of his fatal cases, with one exception, was due to septic encephalitis, and he commented on the striking contrast between the condition of the patient before operation and that after the surrounding brain had been traumatized and infected in an attempt to drain the pus. He further stated that in such an instance the whole process of reencapsulation must be repeated by the brain tissues if the patient is to survive. However, no mention was made of finding extracapsular suppurative encephalitis or necrosis coexistent with an encapsulated abscess for which operation had not previously been performed. It is not known whether he encountered this condition. Adson and Craig [5] and Grant,[8] in their respective reports of large series of cases, do not describe this condition. Penfield, in a personal communication to Adson and Craig, stated, in reference to the formation of the capsule, that the course of the abscess, if drainage is not established, depends on the nature and virulence of the organism, and that if an insufficient wall or capsule is not formed, spreading encephalitis with edema of the brain may quickly terminate the patient's life. It is believed that this statement was not meant to apply in any sense whatever to a well encapsulated abscess.

Were a fairly wide-open exposure, which would allow of proper inspection, made at operation for abscess of the brain and were com-

3. Mosher, H. P.: Personal communication to the author.

4. Bagley, Charles, Jr.: Brain Abscess with Pathological Observations, Surg., Gynec. & Obst. **38**:1-13 (Jan.) 1924.

5. Adson, A. W., and Craig, W. McK.: The Surgical Management of Brain Abscess, Ann. Surg. **101**:7-26, 1935.

6. Cahill, Harry P.: Twelve Cases of Cerebral and Cerebellar Abscesses Drained by the Mosher Wire Gauze Cone, Tr. Am. Otol. Soc. **17**:42-66, 1925.

7. Coleman, C. C.: Reduction of Mortality of Brain Abscess by Simple Methods of Treatment, South. M. J. **23**:484-487, 1930.

8. Grant, F. C.: The Mortality from Abscess of the Brain, J. A. M. A. **99**: 550-556 (Aug. 13) 1932.

plete reports made of autopsies in the fatal cases, no doubt a coexisting, noncommunicating, extracapsular suppurative or necrotic process would be found in the brain substance in a number of cases. Considering the uneventful course in the two cases here presented, it is believed that recovery would take place in many such cases. Mosher stated that the possible presence of the associated extracapsular necrosis and suppuration of the brain may have been responsible for some of the fatalities in cases in which his drain was used.

REPORT OF CASES

My first case has already been reported;[9] so only a brief review of this will be made. Following the precepts of Macewen and Eagleton, a more detailed report of my second case will follow.

Case 1.—A woman aged 45, referred to me by Dr. Foster Kennedy, was seen at the Manhattan Eye, Ear and Throat Hospital. A nasal infection developed in the last week of March 1932. On April 1 there was severe pain in the left ear. Myringotomy was performed, but the pain continued. On April 3 the patient suffered from severe headache and vomiting. Two days later rigidity of the neck developed, which became more pronounced. There was diminution of the right abdominal reflex, and a positive Kernig sign was elicited. A diagnosis of meningitis was made. Lumbar puncture showed a cloudy fluid. Antimeningococcic serum was administered. Culture of the spinal fluid was negative. Lumbar punctures were made on April 6 and 7. On April 8 the temperature dropped from 105 to 96 F. On April 9, erysipelas of the face developed, which lasted a week. Discharges from the ear and nose showed Streptococcus haemolyticus. The patient's general condition improved, and the meningeal symptoms cleared, although on April 10 the patient suffered from severe headache and vomiting. On April 17 to 20 neurologic examination showed slight anomia, slight flattening of the lower part of the right side of the face and diminution of the right abdominal reflex. There were slight fulness of the veins of the fundi, and a defect in the upper quadrant of the visual field. The patient's general condition improved, but the headache persisted. The temperature became less but never returned to normal. Anomia continued. Lumbar puncture showed 70 lymphocytes. The meningeal signs cleared. Some pain was felt behind the left ear, and there was a profuse discharge on two occasions. Roentgenograms showed some softening in the region of the mastoid antrum. A diagnosis of probable subdural abscess with possible abscess of the brain was made.

Mastoidectomy, performed by Dr. Ross Faulkner on April 20, revealed an eburnated mastoid, with practically no cells. Exposure of the lateral sinus gave negative results. However, soft necrotic bone was found in the roof of the aditus. The dura was exposed. It was tense and did not pulsate. No pathologic process pertaining to the subdural space was found until the basilar dura was elevated; then there was a discharge of pus. Repeated elevations of the dura were followed by the evacuation of more pus each time. This pathologic process, coupled with

9. King, Joseph E. J.: Brain Abscess: External Rupture of "Capsule" with Pericapsular Brain Necrosis, Ann. Surg. **101**:190-200, 1935; The Treatment of Brain Abscess by Unroofing and Temporary Herniation of Abscess Cavity with the Avoidance of Usual Drainage Methods, Surg., Gynec. & Obst. **39**:554-568 (Nov.) 1924.

symptoms and signs of a lesion involving the left temporosphenoid area, made one suspect and diagnose the presence of an abscess of the brain in this region with evacuation through the area of the mastoid. The leukocytic and polymorphonuclear counts on April 22, 23 and 24 were: 27,300 and 90; 22,100 and 89, and 19,600 and 80, respectively. The results of the previous neurologic examination, with the Babinski sign and ankle clonus on the right side, an increase in the tortuosity of the veins and drowsiness, were sufficient evidence to warrant the diagnosis of an abscess in the left temporosphenoid area.

Operation was performed on April 25. A small opening was made in the left temporal region, rather high up on account of the mastoid wound. A cannula directed into the temporosphenoid lobe failed to meet with the resistance offered by a capsule. Thick greenish yellow pus, however, was recovered by aspiration. A section of bone between the trephine opening and the mastoid wound, about 1½ inches (3.8 cm.) in diameter, was removed. The dura was fixed to the cortex by electrocoagulation. The cortex was somewhat injected. There was an area of underlying softening. Removal of the cortex at this site by suction revealed necrotic brain substance and, deeper in, actual thick yellow-green pus. After removal of this material by suction, a shriveled, collapsed, thickened capsule of an abscess came into view. It was floating freely in pericapsular pus except at the base, where it was firmly attached to the basilar dura at the site of spontaneous rupture. No utilization of the capsule could be made for the purpose of drainage. It was therefore excised, leaving the immediate basilar attachment to the dura. The capsule was empty, except for a thin layer of thick, inspissated greenish pus plastered onto the inner wall of the capsule. All pericapsular necrotic brain tissue and pus were removed by suction until the brain substance seemed to have a normal appearance. The ventricle was not entered. The cortex, for a depth about ½ inch (1.3 cm.), was not involved in the necrosis. No method of drainage to meet the requirements of this condition had ever been described; at least none was known to me. A "handkerchief" of iodoform gauze was depressed into the existing excavation in the brain, which was loosely packed or stuffed with fluffed iodoform gauze in the same way that the Mikulicz drain is introduced. Copious gauze dressing and treatment with a diluted solution of sodium hypochlorite were employed.

The iodoform gauze was gradually removed on the sixth day, accompanied by gradual herniation, which was mild. The surface of the brain substance presented the distinct appearance of fibrosis and offered resistance to pressure —a distinct contrast to the soft friable brain substance seen at the time of operation.

There was slight herniation, the surface reaching but little above the level of the skull. Lumbar puncture, performed on May 24, with removal of 15 cc. of clear fluid, diminished the size of the hernia, and its level subsided. The granulating surface was completely epithelized. The patient was discharged on the fiftieth postoperative day. The area was completely healed over on the sixty-fifth day.

On November 7, a radical operation was performed on the left antrum by Dr. Faulkner.

On April 12, 1933, a plastic operation was done on the scalp, with excision of the scar.

At present the patient is completely recovered, except that at times there is misuse of a word.

CASE 2.—L. B., a surgeon aged 55, was referred to me by Dr. Leopold Stieglitz and by the patient himself.

History (from notes by the patient).—The patient had had attacks of severe frontal pain since childhood. He was treated for a long time during childhood for exophoria and wore prisms from about 1895 to 1900. He had headaches in the morning, which increased in intensity during his attendance at medical school. This was especially noted on the left side. In 1910 the middle turbinate on the left side was removed, and the patient had severe attacks of left frontal sinusitis. The question of an external operation was then discussed, but this procedure was rejected. From 1910 to 1918 he was under treatment for sinus disease, during which time numerous punctures of the antrum, with irrigations, were done. In 1918 an intranasal operation to relieve the frontal headache was done. During this procedure the septum was resected, and the ethmoid sinuses were opened and drained. During the operation marked hemorrhagic extravasation of the conjunctiva was noted. There was increase of pain in the region of the left orbit and the left frontal area after the operation. Five days after the operation there were marked edema of the eyelids and protrusion of the bulbus oculi. The diagnosis of an extra-orbital exudate was made. A radical external operation on the frontal sinus was performed six days after the intranasal procedure. A large portion of the mesial osseous wall of the orbit was removed. The incision was closed, with a drainage tube passing down through the naso-frontal duct into the nose.

The frontal headaches were somewhat improved after the operation, but the headaches in the sphenoid area became unbearable.

In the interval between 1918 and 1928 a large number of intranasal procedures were done. Portions of the ethmoid bones were removed. On several occasions openings into the sphenoid sinuses were made as well as permanent openings into both antrums. The tonsils were also removed. In 1920 mastoidectomy was performed on the left side. The operation was complicated by pneumonia type I. Serum sickness developed, although desensitization had been carried out. In 1928 a diagnosis of "intranasal neuralgia" was made by a well known rhinologist, the neuralgia being given as the cause of the persistent pain in the left orbit and the left frontal region. The patient believed that a focus of pus existed somewhere in the left ethmoid region and that this focus was being poorly drained. He therefore importuned Dr. Stuart L. Craig to continue his examinations. These efforts were rewarded by the finding of a passage which led upward and apparently into a para-orbital cell below and to the outer side of the frontal sinus. This position of the probe was confirmed by roentgenograms. Thereafter the treatment consisted in keeping this tract open so as to allow the drainage to continue. Nevertheless, there was a persistence of continuous headaches, which were especially severe in the morning, and intense boring pain was felt in the left orbit. These symptoms suggested to the patient that there were inflammation and breaking down of the bone. In 1930 to 1931, believing that his condition would be improved in a warmer climate, he went to the southern part of California. Improvement did not follow his residence there. In fact, during this stay he had numerous attacks characterized by swelling of the lids of the left eye, especially in the region of the inner canthus. In the winter of 1932-1933 he had marked symptoms of radiculitis of the left lumbar region, with pain radiating down both legs, especially in the left. These pains lasted for about four months.

For several years the patient had been accustomed to pass an applicator into the tract in order to relieve the pains in the frontal and ethmoid regions to some extent. He had noticed that a modicum of relief followed gentle insertion of the nasal probe into this tract with slight movements of the probe. In May

1934 he stated that he was "shocked to find one day that the probe passed readily upward without interference far beyond the probable upper level of the frontal sinus." As this event was unattended by any apparent deleterious effect, and for a number of reasons, the experience was not related to his physician until July 1934.

During July and August 1934 he observed that there were "increasing weakness of the right hand, attacks of pain in the joints, excessive perspiration on exertion, two attacks of vertigo and at least three attacks of fever lasting several days."

In September 1934 he realized that intracranial intervention was necessary, his conclusion being based on the febrile attacks, the increasing weakness of his right hand and the increase of headaches and pains in the head.

On Sept. 29, 1934, a consultation was held in the patient's apartment. Drs. Stieglitz, Kennedy, Craig and Neal and I were present.

Neurologic Examination (Dr. Foster Kennedy).—"The patient's trouble was in the left frontal and temporal lobe. The diagnosis made was abscess in the left frontal region, with the extension from that implicating in some way the left temporal lobe. My reason for saying this was that he had weakness of the lower part of the right side of the face on smiling and on expressing emotions. At the same time, when sending for an ophthalmoscope, he could not remember the name of the man who had been his assistant in practice for many years. That was the first thing that made me know he had anomia. He had weakness of the right abdominal reflex as compared with the left, and weakness of the right grasping reflex as compared with the left. I could find no change in the plantar reflexes. He was perfectly well oriented and inspected his own x-ray films with knowledge, insight and self-restraint. The left fundus was a little blurred. The right was normal. There was no change in the visual fields."

Roentgenographic Examination.—Roentgenograms were made on September 27 by Dr. Dunn after the passage of probes by Dr. Neal into the left nares upward and backward, one being directed toward the sphenoid region and the other toward the ethmoid region. The films showed the probes in situ. In the lateral (fig. 1) and anteroposterior views the anterior probe was seen to pass through a perforation in the ethmoid horizontal plate for a distance of 4.5 cm. into the left frontal lobe. This position of the probe was readily seen in the lateral stereoroentgenograms.

The bone was observed to be necrotic from a point about 0.5 cm. anterior to the opening through which the probe passed, backward toward the sphenoid sinus for a distance of 2.5 cm. The remainder of the bony plate forming the superior plate or wall of the sphenoid sinus appeared to be in good condition. One could not tell exactly the size of the opening in the ethmoid bone, but it was sufficiently large to allow the passage of the probe. The lower probe passed more backward, into the region of the lower part of the sphenoid bone. There were cloudiness and an indefinite haziness in the frontal region. The antrums were fairly clear in the lateral films. In the anteroposterior view (fig. 2) the left antrum appeared to be clear, while the right was cloudy. The latter films also showed that some operative procedure had been done in the area of the left frontal sinus. The two probes likewise could be seen. The anterior probe, after passing up through the ethmoid region, curved or bent somewhat outward, its tip being approximately 2 cm. from the midline. The history of long-standing involvement of the frontal, ethmoid, and sphenoid sinuses (about seventeen years), the roentgenograms showing the probe passing through the ethmoid bone into the

left frontal lobe, the history of the ready passage of the probe without marked intracranial episode, the presence of the severe, prolonged and sustained pain in the head, the history of repeated discharge of pus from this region and Dr. Kennedy's findings led one to suspect the presence of an old, chronic abscess of the brain in the left frontal region, which had partly evacuated itself or had been evacuated through the ethmoid region into the nose.

It was decided that it would be advisable to have the patient or Dr. Neal insert a small cannula into the opening through which the probe had been passed, and if the cannula passed readily, injection of a small amount of air should be done to determine the presence, if possible, of such an old, chronic abscess. A small cannula was placed in the opening of the ethmoid region and passed upward rather easily, in a manner similar to that of the probe. Injection of air was done slowly, with a small syringe. After a few cubic centimeters of air

Fig. 1 (case 2).—Lateral roentgenogram showing a probe (*A*) passed through an opening in the necrotic horizontal plate of the ethmoid bone for 1⅞ inches (4.7 cm.), ⅜ inch (0.9 cm.) beyond the inner wall of the abscess cavity shown in figure 3. The second probe passed toward the sphenoid sinus.

had been injected, the patient stated that he could feel a little "tightness" or slight "fulness" in the left side of his head. The cannula was therefore withdrawn; the patient walked to the roentgenographic room, and stereoroentgenograms were made, both anteroposterior and lateral views. The films showed the presence of a multilocular cavity, which was assumed to be a partially collapsed abscess cavity. In the lateral view (fig. 3) the anterior cavity appeared to be almost vertical, extending upward from the perforation in the ethmoid bone for 2.5 cm., and measuring 2 cm. in its greatest diameter in the lateral direction. This air shadow was the shape of a balloon or of a small fig. Its most anterior portion was 8 mm. from the inner table of the skull. The second air shadow was ovoid or somewhat the shape of a drawn-out bird's egg, being rounded at both ends. It lay in a horizontal direction, practically at right angles to the first cavity or air

shadow. It measured 3.5 cm. horizontally and 2 cm. vertically at its greatest width. The posterior extremity of this air shadow was about twice the size of the anterior extremity; i. e., the small end was directed forward. The second air shadow was more distinct than the first. Whether this was due to the fact that more air was present in the upper horizontal air cavity or whether the wall of the lower vertical one was thicker was not known. Near the anterior pole of the second or horizontal cavity it could be seen that the lower cavity overlapped the upper one, both in the flat roentgenogram and in the stereoroentgenogram. The overlapping of the wall of the one cavity on the other was very definite and was shown by the denser air space, measuring horizontally about 0.5 cm., and vertically about 1.2 cm. (This later proved to be the communication between the two abscess cavities.)

Fig. 2 (case 2).—Anteroposterior roentgenogram showing a probe passed through an opening in the ethmoid bone into the left frontal region.

In the anteroposterior view (fig. 4) two distinct air cavities were likewise shown. The horizontal, or second, cavity was seen more distinctly than the first, as was the case in the lateral view. The first, or anterior, air chamber or cavity measured 1.5 cm. transversely and overlapped the second cavity. The second air cavity was likewise somewhat balloon shaped and measured 1.5 cm. laterally and 2 cm. vertically. There was a trace of air directed downward toward the ethmoid region, where it lost itself. The two air cavities, superimposed with the prolongation of air downward toward the ethmoid region, somewhat resembled the shape of a small tennis racquet. The lower limit of the central portion of the second cavity was 6 mm. above the supra-orbital ridge, and in the lateral position it was about halfway between the inner and the outer canthus. The center of this cavity was 3.5 cm. from the midline. The pineal gland could be distinctly seen, with possibly a slight shift toward the right.

Diagnostic Opinion.—From the history, physical findings and roentgenograms, it was concluded that there was present in the left frontal lobe a multilocular, or multiple, abscess of the brain, probably of long standing. It was assumed that the abscess had at least two fairly distinct connecting cavities, the posterior one of which probably was secondary to the anterior one and probably was an extension from it.

Examination of the Blood (Sept. 27, 1934).—The hemoglobin content was 92 per cent. The white cells numbered 10,400, with 79 per cent polymorphonuclears (segmented 75 per cent, staff 3 per cent and basophil 1 per cent), 1 per cent lymphocytes and 3 per cent monocytes.

Fig. 3 (case 2).—Lateral roentgenogram after the injection of air into the abscess cavity. *A* indicates the smaller anterior cavity connected with an opening in the ethmoid bone by a fistulous tract or stalk, and *B*, the larger posterior horizontal cavity connecting with and overlapping the anterior cavity at *C*.

The patient was admitted to the Harbor Hospital for operation on Oct. 2, 1934, with a temperature of 99.4 F., a pulse rate of 80 and a respiratory rate of 20.

Operation.—From observations and measurements on the roentgenogram the anterior wall of the first or anterior abscess was located at a depth of 1 cm. from the inner table of the frontal bone. It was decided to corroborate this

information definitely by making a small trephine opening over the supra-orbital ridge at the proper position and inserting a brain cannula through a small nick in the dura. A straight vertical incision about 2.5 cm. in length was made over the left side of the forehead, perpendicular to the central portion of the eyebrow. Through this incision an opening was made in the skull just above the supra-orbital ridge, the opening being about 1 cm. in diameter. The cannula was inserted through a small incision in the dura. It was passed directly backward and, on the first puncture, at a depth of 1 cm., it met with firm resistance offered by the capsule of the abscess (fig. 5).

After the exact position of the abscess had thus been determined, it was considered advisable that the operation which was to be done by Dr. Craig should be performed first and that the operation for the abscess should follow. The small

Fig. 4 (case 2).—Anteroposterior roentgenogram showing the two cavities seen in figure 3. The lower inner anterior cavity (*A*) connects with the opening in the ethmoid bone by a fistulous tract or stalk (*C*).

nick in the dura was sealed off by electrocoagulation, and a plug of cotton was placed in the small trephine opening. This was done to block off the subdural space and prevent the spreading of infection into it. The incision was then carried down through the old scar, which resulted from the previous operation on the frontal sinus. This scar was excised, and the scalp flaps, three in number, were reflected and held with self-retaining retractors. This exposure gave adequate access to the remnants of the frontal sinus and the ethmoid and the sphenoid regions.

The operative procedure, performed or carried out by Dr. Craig, was described by him as follows:

An incision in the ethmoid region was made following the approximate line of the old scar. This incision was carried down to a probe which had been

passed into the old sinus opening. The previous operation was found to have been well completed. The orbital plate of the ethmoid had been completely removed, the ethmoid well exenterated and the sphenoid widely opened.

The diseased area consisted of necrotic bone lying against and including the basal plate of the skull, a part of which came away as a sequestrum on both sides of the opening through the dura. A posterior ethmoid cell lying in the angle between the orbit and the basal plate was found to contain infection, and a cell of the middle ethmoid, very high up, was also infected. All diseased bone was removed, and the ethmoid cells were completely eliminated. There was no necessity for interference with the sphenoid or with the antrum.

On completion of this procedure, the nasal cavity of the left side was well packed off with strips of iodoform gauze so as to prevent leakage of blood into the nasal cavity. (A postnasal plug had previously been introduced.) The trephine opening which had previously been made was then enlarged, first in a

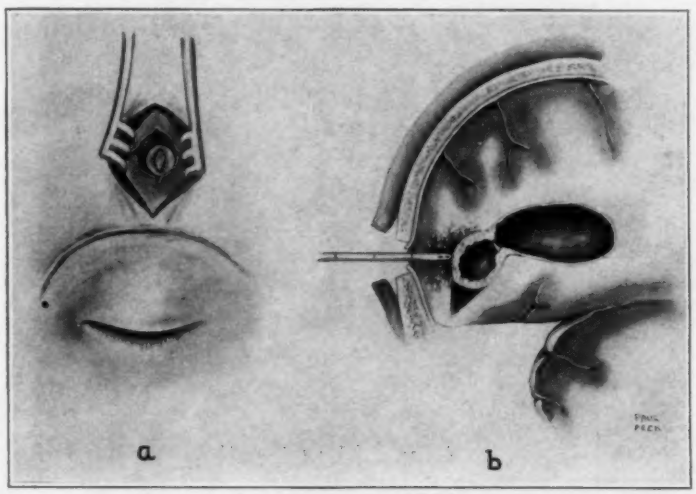

Fig. 5 (case 2).—The trephine opening made in the supra-orbital region over an old scar in the eyebrow, with a small incision in the dura, is shown in *a*. The cannula was then passed through the dural incision and through soft, extra-capsular necrotic brain substance, where it met with firm resistance against the wall of the anterior abscess at a depth of 1 cm., as shown in *b*.

circular manner to about the size of a half-dollar. The dura was fixed to the cortex near the margin of the bone with the electrocoagulation tip and was opened in a stellate fashion; the dural flaps were cut away and discarded. The dural margin was more adequately fixed to the cortex, and strips of iodoform gauze were placed around the bony and dural margins, where they became fixed in position. The cortical surface exposed was about the size of a 2 franc piece. The cortex overlying the anterior portion of the capsule of the abscess was sucked away. Owing to the fixation of the dura to the cortex, there was no tendency for the latter to fall away or droop or sag from the dura. There was no fear, therefore, of soiling or spreading the infection through the subdural and subarachnoid spaces.

At a depth of 1 cm. the anterior surface of the capsule of the abscess came into view. As it was being exposed, it was observed that the brain tissue, especially about the anterior, external and superior portions of the capsule, was necrotic, yellowish and broken down (fig. 6). Nearer the capsule there was thick yellow pus. The anterior half of the anterior capsule was removed (fig. 7). The abscess cavity contained thick yellow pus, without a foul odor. A specimen sent to the laboratory was reported to contain Streptococcus haemolyticus.

Adequate inspection of the cavity could then be done. As the pus was removed by suction and cotton pledgets, an opening about 1 cm. in diameter was seen at the upper posterior pole of the capsule. From the opening the same type of thick yellow pus exuded in a pulsating fashion, corresponding with the heart beat.

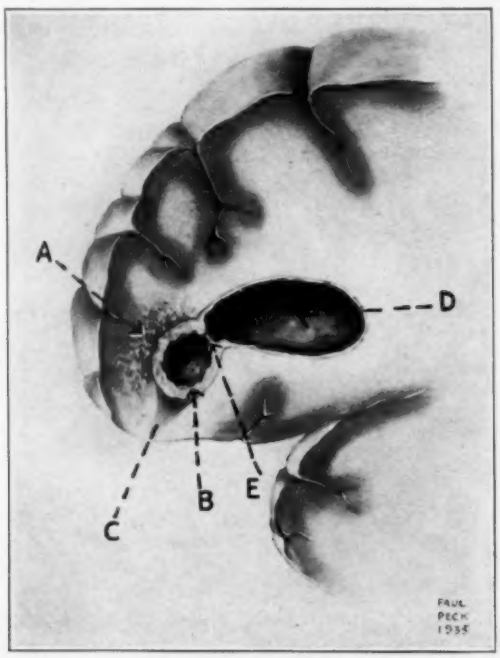

Fig. 6 (case 2).—A schematic section of the lesions, showing extracapsular necrotic and suppurative brain substance (*A*); the very thick wall of the smaller anterior abscess (*B*), with the "stalk" (*C*) leading downward and inward to the opening in ethmoid bone, and the posterior, and larger, abscess cavity (*D*), with a definite, but thinner wall which connects with the anterior cavity through an opening (*E*).

This opening led into a second abscess cavity, which was horizontal in position and similar to the air shadow shown in the roentgenogram. The cavity, which was partly collapsed, measured from about ⅝ to ¾ inch (1.6 to 1.9 cm.) in diameter and about 1¼ to 1½ inches (3.2 to 3.9 Gm.) in length. This capsule was much thinner than the anterior one, showing that the abscess was of more recent origin. The wall of the anterior cavity was about ⅛ inch (0.3 cm.) thick, or perhaps a little thicker, while that of the posterior cavity was about 1 mm. in

thickness. The posterior cavity was therefore evidently an extension from the more ancient, anterior abscess cavity, as a result either of spontaneous rupture backward or of trauma produced by the probe.

The anterior abscess had a "stalk" or tract which led from its lower pole inward, forward and downward to the ethmoid region. It was necessary to remove bone far down toward the nasal cavity in order to uncover this tract and to determine the exact point where it perforated the base of the skull in the anterior fossa. This was found to be the horizontal plate of the ethmoid sinus, in the same position as shown on the x-ray films. Necrotic bone about the opening of this tract was removed. The lumen of the tract was just sufficient to allow the passage of an ordinary silver probe. The shape of the anterior abscess was that of an elongated balloon or an unripe fig, the capsule corresponding to the fig itself and the tract to the stem of the fig. The transverse diameter of the abscess capsule at its greatest width was about 1 inch (2.5 cm.). The wall was

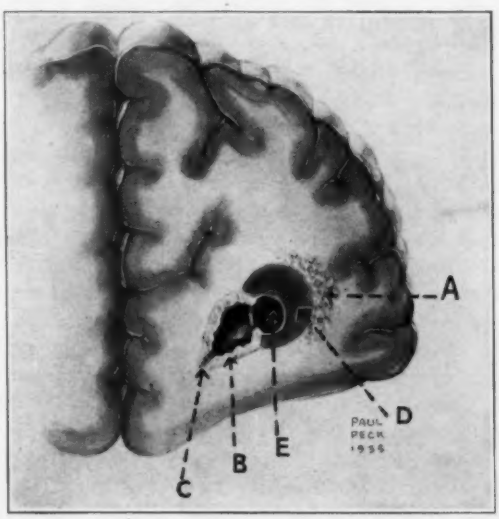

Fig. 7 (case 2).—A schematic section of the lesions, showing where the anterior half of the thick wall of the anterior abscess (*B*) and its stalk (*C*) were cut away and the opening (*E*) about 1 cm. in diameter between the anterior and the posterior (*D*) abscess cavity. A considerable amount of brain substance between the lateral cortex and the abscesses was necrotic and contained pus. No connection between this area and the cavities was detected.

rigid and did not tend to collapse. The anterior wall of the tract was removed, and the posterior half of the tract and its connecting capsule were left attached to the brain substance in order to keep the brain fixed at this point so as to prevent overherniation. The granulating inner surface of the tract was curetted gently and swabbed with phenol and then with alcohol.

The extracapsular necrotic brain tissue and pus were then removed by suction, until the brain substance presented a rather normal appearance. This sucked-out excavation in the brain led back alongside of, and external to, the second or posterior abscess cavity for a distance of about ⅜ inch (0.9 cm.). The exposed lateral wall of the posterior abscess was then removed so as to lessen

the relative depth of the cavity and to afford more adequate drainage. It was expected that the remaining posterior portion of this cavity would move or herniate forward and so "catch up" with the remainder of the excavation in its forward progress.

The procedure was now completed except for the dressing. A small strip of soft iodoform gauze was loosely stuffed into the remaining portion of the posterior cavity. A "handkerchief" of iodoform gauze was then placed over the excavation in the brain and depressed so that it came in contact with the brain substance, and the opening was loosely stuffed or packed with fluffed iodoform gauze in the manner of the Mikulicz drain, except that iodoform gauze was used in place of rubber dam. The nasal and supra-orbital region were also well packed off with iodoform gauze. The flaps were replaced and loosely sutured. A copious gauze dressing wet in a dilute solution of sodium hypochlorite was applied over the entire area and held with a slightly compressing bandage, which passed over the head and the lower jaw. Both eyes and ears were covered well with petrolatum gauze and were included in the dressing. The patient withstood the operation well.

After the operation it was considered advisable to give a blood transfusion. This was done on the operating table by Dr. Eggston. The patient left the operating room in good condition.

NOTE.—In this case two distinct abscess cavities existed. The posterior one had probably existed for not more than three or four weeks, and the anterior one, probably much longer. The posterior cavity connected with the anterior one, and it in turn was connected with the nasal cavity by means of a fistulous tract or "stalk," which allowed both cavities to drain incompletely through into the nasal cavity. (One could compare the situation with a system of lakes drained by a river.) In addition, there was a considerable amount of extracapsular necrotic brain substance and thick yellow pus which did not connect with or drain into the abscess cavity. To complicate matters, the area of the extensive procedure performed by Dr. Craig was in immediate juxtaposition, and was continuous with, the area involved in the intracranial procedure. This was the first time that I have observed this to occur.

Therefore, the questions which arose were: Will the posterior portion of the posterior abscess cavity herniate forward sufficiently to obliterate it? Will the brain hernia proceed forward and project into the nasal cavity? How can one block off the nasal portion from the intracranial portion of the operative area so that proper treatment of the intracranial area with solution of sodium hypochlorite can be effected, and therefore, so that infection can properly be combated? Will it be possible at a later date to remove the packing from the nasal portion of the wound and allow the anterior flap to fall back into position, become adherent and thus successfully block off the intranasal area? These questions could not be properly answered at the time.

Progress Notes.—October 3: At 5 a. m. all of the external dressing was removed. The loose sutures holding the flaps together were removed, and the scalp flaps were gently lifted up. The iodoform gauze packing beneath the flaps was loosened, but none of it was removed. A dressing was so applied as to allow mild herniation. Treatment with solution of sodium hypochlorite was not begun on account of the communication with the nose. The patient's general condition was very good. The pulse rate was 74 and temperature 100.6 F. Mentally the patient was clear and alert. He asked questions about his condition, his left eye, etc. About five hours after his operation he stated that it was the first time in years that he was free from the "old pain" in his head.

At 11 o'clock on the same day the external gauze packing beneath the flaps was loosened and removed. The original iodoform gauze in the depths was not disturbed. There was slight herniation of the brain about the gauze packing in the brain substance and in the abscess cavity, which was as it should be. The head of the bed was elevated to about 15 degrees. The patient's general condition was good, with no rise in temperature and no rigidity of the neck.

October 6: Dressing was done either once or twice a day. Loosening of the two pieces of iodoform gauze, the one in the abscess cavity itself and the other in the extracapsular cavity in the brain substance, was begun. Gauze blocking off the nasal area was not disturbed. The patient's general condition remained good. The temperature varied from 99.8 to 100.8 F., and the pulse rate from 76 to 84. He took his nourishment well, and was mentally alert. The elimination of the bowels was satisfactory.

October 8: All of the original iodoform gauze packings introduced at time of operation, with exception of that blocking off the nasal cavity, were removed. There had been slow and progressive herniation, so that the remnant of the abscess cavity was not more than 1 cm. wide and about 1 cm. deep. The surface of the brain substance had become firmer and more granular. Definite fibrosis had taken place. The small funnel-shaped remnant of the cavity was held open with a wick of iodoform gauze to prevent its collapse in the transverse direction. It was expected that herniation of this remnant of the cavity would be complete by the next day. As soon as it had reached the level of the remainder of the brain surface, herniation could be controlled by catharsis or by lumber puncture, if necessary. Treatment with solution of sodium hypochlorite had been done for the past two or three days without leakage into the nasal cavity. The patient's general condition remained good throughout. The temperature varied between 99 and 100.5 F., the highest temperature being 100.8 F., on the first postoperative day. At the next dressing the last piece of the original iodoform gauze packing in the nasal and ethmoid regions, which was used to block off these areas, was slowly and completely removed. The surfaces were clean and presented a well granulating appearance. Two narrow iodoform gauze strips were then placed as follows: One was seized with a bayonet forceps through the left side of the nose and was drawn out through the left nares, the distal end being left in the ethmoid region; the other was placed overlying the remnants of the "stalk" or tract of the old abscess cavity so that the ends of the two pieces of iodoform gauze were separated from each other about ½ (1.3 cm.) to ⅝ (2 cm.) inch. The posterior orbital contents were then allowed to fall back against this area, so that they could become adherent at this site and thus block off the nasal cavity from the operative site of the abscess, i. e., the site of the slight hernia. The remainder of the wound was loosely stuffed with iodoform gauze. Treatment with solution of sodium hypochlorite was discontinued for twenty-four hours, during which time it was expected that the walling-off process would take place and form a barrier between the two operative sites. Otherwise leakage of the solution into the nose would have produced coughing, which would have been detrimental to the hernia. The patient's general condition remained good.

October 9: The patient awakened in the early morning and removed the external dressing. The packings of iodoform gauze were not disturbed. He was slightly irritable, and it is believed that this irritability was due to cortical irritation produced by the dry iodoform gauze in the absence of solution of sodium hypochlorite. Similar episodes had previously been observed in other cases. The condition of the wound was good. The entire exposed surface of the brain was swabbed with a 12 per cent solution of silver nitrate in order to increase the fibrosis. Treatment with solution of sodium hypochlorite was resumed.

October 10: The intranasal gauze strip was loosened but not removed. The general condition of the wound was good. The apex or the remnant of the abscess was somewhat yellowish and was partly separated and slowly coming away. Another suture was placed over the inner canthus fixing the lower flap to the upper one. This suture, in addition to the one previously placed, partially closed the inner portion of the supra-orbital incision.

October 11: Herniation had extended to just above the level of the skull, but not to the level of the scalp. A strip of gauze directed along the old sinus tract toward the nasal area was removed and replaced. Instillation of solution of sodium hypochlorite did not produce coughing, and the solution did not leak into the nose. Therefore, it was considered that the nasal cavity was completely barricaded from the remainder of the wound.

October 20: The wound had been dressed daily. The internal and external scalp flaps had become completely fixed to the lower flap. The granulating surface of the brain was somewhat of the shape of an arrowhead and about 1 inch

Fig. 8 (case 2).—Photograph of the patient on the twentieth day after operation, showing the healed incision through the eyebrow and alongside the nose. There remains a small depressed granulating area which healed on the thirty-fifth day, the day of discharge. The surface of the brain never quite reached the level of the skull.

long in the vertical direction and ½ inch (1.3 cm.) wide. The margins of the wound had become covered with epithelium extending from the edges of the scalp. The small tract overlying the old "stalk" of the abscess, and which extended beneath the medial flap toward the nasal area, was intentionally kept open in order to be assured that no pocketing could take place.

October 22: Epithelization of the granulating surface had increased (fig. 8). Only a small dressing was required. Less frequent instillations of solution of sodium hypochlorite were used. The patient's general condition was good. The temperature varied from 98 to 99 F. and had done so for three or four days. Diplopia was not present. There was only a slight overlapping. The patient had gained weight and was able to receive visitors and use the telephone.

October 29: The wound had almost healed except for the small tract beneath the medial flap over the area of the "stalk." The patient had read the newspaper for four days. On the preceding day he had shaved himself and on the present date he sat up out of bed without any discomfort or dizziness.

November 5: The frontal wound had completely healed except for a small area in the lower inner corner, which was about ¼ inch (1.3 cm.) deep and was the remnant of the old tract.

November 7: The patient had been out of bed most of each day. The wound had completely healed, five weeks after the operations. His general and local conditions were good. No headache, dizziness or other complaints developed. The appetite and mentality were good. There was slight edema of the upper left eyelid. A pulsating oval depression, about 1 inch in the vertical direction and about ⅝ inch (2 cm.) in the transverse direction, was present in the left frontal region. The central portion of the depressed area was about ½ inch (1.3 cm.) below the level of the scalp. The incision through the eyebrow healed kindly, leaving a narrow scar, which was but slightly depressed and produced little deformity. A small patch was to be worn over this area until a plastic operation could be performed on the scalp. The original wound, which was extensive and involved the frontal, ethmoid and intranasal areas, healed more rapidly and with less degree of herniation, without lumbar puncture, than any other which had been observed by us.

The patient was discharged to his apartment on November 8.

Follow-Up Notes.—The patient was seen a few times after his discharge from the hospital, and after a short time he resumed his practice.

On Feb. 16, 1935, a small subperiosteal pocket over the outer margin of the cranial defect was incised with the area under local anesthesia, and two loose pieces of bone wax, which had been used at the time of the original procedure, were removed. There was a small amount of pus about them. The small wound was packed with an azochloramide oil gauze wick, and after a few dressings it promptly healed.

At the present time the patient has completely recovered. He has no complaints and attends to his practice.

METHOD OF DEALING WITH THE CAPSULE

In case 1 the capsule could not be utilized in any manner in the drainage of the infected lesions in the brain. In fact, had it not been anchored at the site of the perforation in the basilar dura, one would have found it floating in the pericapsular pus, as in case 30 described by Macewen. It was really a foreign body. This is the first and only case in which the capsule has been removed and discarded, and in this instance this was done solely for the reason that no use could be made of it.

In case 2 it was necessary to remove the anterior half of the capsule of the anterior, or older, abscess in order to deal adequately with the coexisting communicating abscess cavity. It was also necessary to remove the anterior half of the "stalk" or tract leading down to the ethmoid bone in order to deal with the infection which it contained. It was not only unnecessary but undesirable to remove the posterior half

of the anterior capsule and its "stalk" for the reason that herniation of the brain at this site would not be advantageous. There was no extracapsular necrotic material at this particular region. The posterior surface of this capsule was firmly fixed to the surrounding brain, and the "stalk" was even more firmly fixed to the dura. The continuation of this fixation was desired for the following reasons: 1. It was needed to serve as a barrier to prevent infection at this site from entering the subdural and subarachnoid spaces; (2) the heavy thick posterior wall gave additional strength to the brain substance at this point and tended to prevent overdistention or rupture of the anterior horn of the lateral ventricle, and (3) by prevention of herniation at this site compensatory herniation of the posterior cavity would naturally ensue. It was desirable to have this process occur.

Our expectations and hopes were realized in the manner in which the herniation occurred. That portion of the brain substance which remained after the extracapsular pus and necrotic tissue had been removed by suction, together with the thinner-walled capsule of the posterior abscess, herniated forward just sufficiently to obliterate them. Herniation to the level of the surface of the scalp was not desired and never occurred, even in the absence of lumbar punctures.

In the usual case of uncomplicated, encapsulated abscess of the brain, i. e., in which the capsule is not detached or in which there is no extracapsular necrotic brain substance or pus, only the presenting portion of the capsule should be removed after it has been exposed. The pus in the cavity is removed by suction, and the cavity is wiped out. The inner surface of the capsule is inspected to determine its size and the possibility of an extension into a secondary pocket. It is then gently stuffed or packed with a layer of iodoform gauze placed as a Mikulicz tampon.

The following events then take place: With the oncoming increase in the intraventricular fluid, the floor of the abscess will move outward, delivering the iodoform gauze packing with it. This gauze is gradually removed after being moistened with hydrogen peroxide. The thickened capsule of the abscess then serves as a limiting barrier with definite resistance and tends to prevent overherniation. It also gives greater resistance to the surface of the slight hernia and lessens the likelihood of leakage of cerebrospinal fluid from the ventricle. The capsule is not removed. Its surface becomes covered with granulation tissue and later with epithelium. It becomes a part of the general scar tissue at the operative site.

As soon as the herniation of the cavity has advanced to or about the level of the skull, the probability, or even the possibility, of the formation of a secondary pocket from this abscess does not exist. At

this stage a lumbar puncture should be done if it is necessary, and thereafter it should be repeated sufficiently often to prevent overherniation. The marked herniation advocated and described in my original paper is not necessary and is not desired for the reason that leakage from the ventricle would be more likely and the period of convalescence would be longer. It has been found that herniation can be easily, readily and safely controlled.

My reason for discussing this phase of the subject in this paper is that some writers have evidently concluded that removal of the capsule in toto in the usual case is advocated by me, while others believe that excessive herniation is still advised.

In my last paper it was suggested that the necrotic brain substance found in the early or first stage of abscess of the brain might be removed by suction followed by tamponade of the excavation with iodoform gauze. Two patients with this condition have been operated on in this manner. In each, the lesion was metastatic from a suppurating focus in the lungs. One, a surgeon, has recovered with rapid disappearance of hemiplegia, homonymous hemianopia and hemianesthesia and almost complete disappearance of aphasia. The other is now convalescing in the Bellevue Hospital. These cases will be reported on in a subsequent paper.

SUMMARY

Detailed reports of the pathologic process associated with abscess of the brain, including its variation found at operation or at autopsy, would improve the knowledge of the subject and would help to determine the proper procedure to be used in a given case.

More adequate information concerning the actual condition at operation, especially pertaining to the presence or absence of extracapsular suppuration and necrosis, can better be ascertained by the "open" method of dealing with the abscess than by the "closed" procedure. Some patients, in whom the extracapsular infection is present and on whom the described method of operation is used, would have a better chance of recovery.

Two cases of abscess of the brain associated with extracapsular necrosis and suppuration are reported. Recovery occurred in both cases after operation.

The method of dealing with the capsule is described, and retention of the capsule or a part of it, if possible, is advocated.

Brief mention of operation and the results in two cases of metastatic abscess of the brain is made.

THE INCIDENCE OF GALLSTONES IN SWEDEN

THE CORRELATION OF GALLSTONES WITH VARIOUS DISEASES AND PATHOLOGIC CHANGES

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STOCKHOLM, SWEDEN

Publications have been issued from the different countries regarding the incidence of gallstones and the correlation of gallstones with various diseases. Up to the present there has been no such publication from Sweden, and it was principally for this reason, on the request of Prof. F. Henschen, of the pathologic department at the Karolinska Institute, that I undertook the preparation of this article.

MATERIAL

This treatise embraces the incidence of gallstones observed at autopsy at St. Erik's Hospital, Stockholm, Sweden, during a period of ten years, from the beginning of 1925 to the close of 1934, clinical symptoms observed in cases of gallstones, taken from the records of this hospital, and data on the distribution of the clinical cases of gallstones in Sweden during the same period, obtained from the annual reports of the public hospitals.

The postmortem study was based on 6,575 autopsies, of which 3,351 were performed on females and 3,224 on males, there being 2 per cent more females than males. Not only was the material equally divided between the sexes, but the records of the cases had been carefully and similarly kept—a valuable factor which renders the material particularly suitable for statistical adaptation.

The clinical reports in the majority of cases were fairly well detailed, but in many instances the histories were scant, and sometimes, owing to the condition of the patient, could not be taken at all. Because of this, the statement of clinical symptoms gathered from the records contained in the clinical reports will be unavoidably limited to some extent. Regarding pregnancy, the reports were too sporadic to admit of any statement as to the correlation with gallstones.

As it is compulsory for each hospital to register carefully all cases of sickness, figures taken from these reports may undoubtedly be

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regarded as an exact recording of the incidence of gallstones at that particular hospital. As to whether or not they should be considered as demonstrating the incidence of gallstones in that particular neighborhood will be dealt with when I consider the results of my investigation.

METHOD

The investigation was executed tabular-statistically, i. e., all cases of gallstones were tabulated for each year and each case in which autopsy was performed has been recorded as to (*a*) the age and sex of the patient; (*b*) the type, number, size and position of the stones; (*c*) the contemporary changes in the bile, gallbladder and biliary ducts, and (*d*) other diseases and changes of interest (constitutional diseases, disturbances in the transformations of calcium and pigment, disturbances in motility in the bile ducts and in connection with the local and general circulation, local and general infectious diseases, malformations, etc.). Clinical symptoms have been recorded in each case as to (*a*) the sex of the patient and the time when each symptom appeared; (*b*) whether the symptom appeared once or whether it was repeated and (*c*) whether, as regards the patient in question, only one symptom occurred; if more, the order of appearance, and whether they recurred in immediate sequence or at intervals. These data should be considered as preliminary material.

A part of the investigation as to the incidence of gallstones at St. Erik's Hospital and the distribution according to age is based on material recorded at this hospital from 1925 to 1932, collected by Dr. T. Bruce, of Stockholm.

INCIDENCE OF GALLSTONES IN STOCKHOLM

From table 1 it is seen that gallstones have been found frequently at autopsy at St. Erik's Hospital. However, as the patients were older (chart 1), the figures shed no light concerning the incidence of gallstones among the inhabitants of Stockholm in general. I have therefore calculated the percentage of incidence within the various age groups, i. e., from 0 to 15 years, from 15 to 50 years and after 50 years, and I have obtained records from Stockholm's Statistical Bureau as to the average number of inhabitants of both sexes in Stockholm within the aforementioned age groups for the years from 1925 to 1934, inclusive. Thus, taking into consideration age and sex, I have been able to estimate the incidence of gallstones among the inhabitants of Stockholm as follows: Of the 551,618 inhabitants, 58,205 should have gallstones, i. e., 10.5 per cent. Accordingly, every tenth inhabitant of Stockholm should have gallstones.

CLINICAL SYMPTOMS

How many patients with gallstones manifest clinical symptoms?

Clinical symptoms were noted in approximately 25 per cent of the patients, i. e., in 4.9 per cent of those who came to autopsy. The incidence in males and females was relatively equal. Death ensued in 6.4 per cent of the cases of gallstones (with complications), i. e., 1.2 per cent of the cases in which autopsy was performed. Fatalities occurred in 5.5 per cent of the females, i. e., in 1.5 per cent of the females who came to autopsy, and in 8.3 per cent of the males, i. e., in 1 per cent of the males who came to autopsy. According to the calcu-

TABLE 1.—*Incidence of Gallstones, Cited from the Autopsy Records at St. Erik's Hospital*

	Autopsies			Cases of Gallstones					
				Females		Males		Total	
Year	Females	Males	Total	Number	Percentage	Number	Percentage	Number	Percentage
1925	221	240	461	54	30.3	13	5.4	67	14.5
1926	271	286	557	82	30.3	31	10.8	113	20.3
1927	339	333	672	61	18.0	30	9.0	91	13.5
1928	276	310	586	62	22.5	21	6.8	83	14.2
1929	286	304	590	71	24.8	38	12.5	109	18.5
1930	365	331	696	115	31.5	49	14.8	164	23.5
1931	392	358	750	106	27.0	52	14.5	158	21.1
1932	399	354	753	108	27.0	44	12.3	152	20.2
1933	362	328	690	121	33.4	59	18.0	180	26.1
1934	440	380	820	123	28.0	48	12.6	171	20.8
10 years	3,351	3,224	6,575	903	27.0	385	12.0	1,288	19.6

Incidence of gallstones in the whole material: 19.6%, i. e., in every fifth case
Incidence of gallstones in females: 24.0%, i. e., in every fourth case
Incidence of gallstones in males: 12.0%, i. e., in every eighth case
Proportion of incidence in females and males: 2¼ : 1

lation of incidence among the inhabitants of Stockholm, 2.5 per cent of the inhabitants, or one fortieth, had symptoms.

Records of clinical symptoms have been obtained, as stated previously, from the histories of patients who came to autopsy. With due allowance for inaccurate notation of symptoms, for obvious reasons I will refrain from attaching too much importance to the figures as regards either the total incidence of the clinical symptoms or the incidence of the separate symptoms. As regards the latter, the figures so decidedly point in a certain direction that I cannot refrain from drawing attention to them.

Various Symptoms and How They Appear.—As may be seen from table 3, "typical painful attacks" were the most frequently recorded symptom. They were present in 217 patients, and in 22, or one tenth, they were the only symptom. In 170 of the 217 patients, or eight tenths,

signs of cholecystitis and cholangeitis developed sooner or later. The latter symptoms appeared as a rule in immediate connection with "typical painful attacks." In those persons in whom "typical painful attacks" were the only symptom it was exceedingly common for only one attack

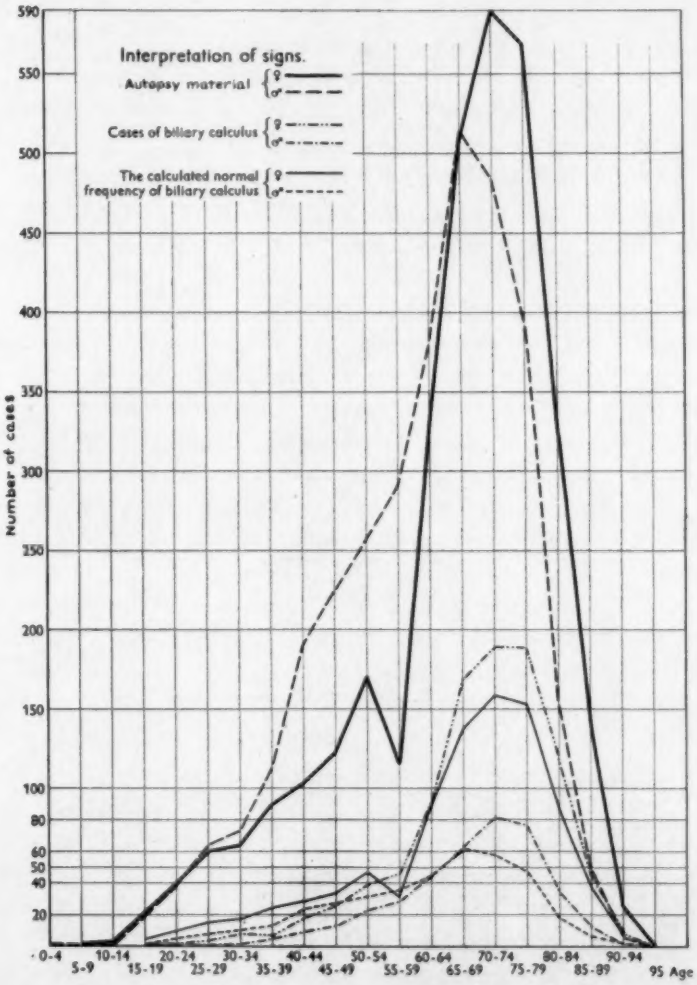

Chart 1.—The distribution of autopsy material and cases of biliary calculus according to age and sex.

to occur during the patient's life, while in persons in whom signs of cholecystitis and cholangeitis later appeared more frequent attacks were the rule. In the majority of those who had only one "typical painful attack," there developed later signs of cholecystitis and cholangeitis.

TABLE 2.—*Clinical Symptoms in Cases of Gallstones According to Hospital Records*

	Cases of Gallstones			Clinical Symptoms						Cause of Death					
				Females		Males		Total		Females		Males		Total	
Year	Females No.	Males No.	Total No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1925	54	13	67	16	29.6	1	7.9	17	25.4	3	5.6	..	....	3	4.5
1926	82	31	113	13	15.8	4	12.9	17	15.0	1	1.2	1	3.2	2	1.8
1927	61	30	91	18	29.5	10	33.3	28	30.8	5	8.2	2	6.7	7	7.7
1928	62	21	83	26	42.0	9	42.9	35	42.5	6	9.7	1	4.8	7	8.4
1929	71	38	109	14	19.7	14	37.0	28	25.7	3	4.2	7	18.4	10	9.2
1930	115	49	164	26	22.6	11	22.4	37	22.6	8	7.0	5	10.2	13	7.9
1931	106	52	158	27	25.5	7	13.5	34	21.5	6	5.7	2	3.8	8	5.1
1932	108	44	152	25	23.1	8	18.2	33	21.7	4	3.7	5	11.4	9	5.9
1933	121	59	180	36	30.0	16	27.1	52	28.9	7	5.8	7	11.9	14	7.8
1934	123	48	171	26	21.1	12	25.0	38	22.2	7	5.7	2	4.2	9	5.3
10 yr.	903	385	1,288	227	25.1	92	24.0	319	24.9	50	5.5	32	8.3	82	6.4

TABLE 3.—*Various Clinical Symptoms* *

Symptom	Total No. of Cases	Sole Symptom	Sex; No. of Cases		Manner of Appearance	
Typical painful attacks	217 (68%)	22 (6.9%)	♀	138 (61%)	Sole symptom.....20	1 attack in 16 cases; several attacks in 4 cases
					Combined with cholecystitis and cholangeitis.....99	1 attack in 28 cases; several attacks in 71 cases
					Combined with dyspeptic trouble.....19	
			♂	79 (36%)	Sole symptom..... 2	1 attack in each case
					Combined with cholecystitis and cholangeitis.....71	1 attack in 16 cases; several attacks in 55 cases
					Combined with dyspeptic trouble..... 6	
Movement pains	2 (6%)	1 (3%)	♀	2 (0.9%)	Sole symptom..... 1	several attacks
					Combined with cholecystitis and cholangeitis..... 1	several attacks
			♂	0		
Signs of cholecystitis and cholangeitis	189 (59%)	18 (5.6%)	♀	112 (50%)	Sole symptom.....13	
					After "typical painful attacks".....99	
			♂	77 (84%)	Sole symptom..... 6	
					After "typical painful attacks".....71	
Dyspeptic troubles	109 (34%)	53 (16.5%)	♀	98 (43%)	Sole symptom.....51	
					Combined with other symptoms.....47	
			♂	11 (12%)	Sole symptom..... 2	
					Combined with other symptoms..... 9	

* Only one symptom developed in 29.3 per cent of the patients. Several different symptoms occurred simultaneously or one after the other in 70.7 per cent of the patients.

Thus it would seem possible that if the patient had "typical painful attacks," cholecystitis and cholangeitis were almost sure to follow.

In only 18 of 189 patients have signs of cholecystitis and cholangeitis been noted without any record of previous "typical painful attacks." As to whether cholecystitis and cholangeitis can develop without the preceding typical painful attacks as a symptom of the passing or wedging in of the stone, I dare not venture an opinion in view of the aforementioned inaccuracies.

With reference to dyspeptic troubles, it would seem just as impossible to make any statement, because, as has been seen, these need not necessarily have been brought about by gallstones but may have been a symptom of some associated disease.

A symptom has been included here which might be called "movement pains." As the name implies, the term indicates those pains which occur and accompany movement and which disappear when the patient is in repose. They are manifest as light pains or as diffused discomfort in the region of the gallbladder and eventually in the back at the angle of the right scapula or between the right shoulder blade and the spine, or they may occur simultaneously at both places or at only one of them. On careful investigation of the histories of patients with gallstones I have found "movement pains," as I remember now, in 8 of 15 patients. These pains were the patient's earliest symptom of gallstones, and when they appeared there was no sign of infection. This is essentially the reason I have included this symptom in this connection. It has been noted in only 2 patients in this study, and this is probably because the patients had not taken notice of those lesser inconveniences and therefore omitted to mention them to the doctor who took the history. (The diagnosis in both cases was lumbago [?]).

DISTRIBUTION OF MATERIAL ACCORDING TO AGE

When the postmortem material was grouped according to age a well known condition prevailed; namely, the mortality rate was higher in men than in women in the early years, i. e., between the ages of 30 and 55, while it was higher in older women. It is of particular interest to note that the greater part of this material includes persons between 60 and 80 years of age. The distribution of gallstones according to age will be taken up in connection with the question as to at what age stones appear and as to how long new stones can be formed.

In order to determine at what age stones appear and how long new stones may be formed, obviously a comparison must be made between the incidence curves in clinical cases and the normal incidence curves calculated according to the age distribution in the postmortem

material (chart 1). An investigation of chart 1 shows that stones have been known to appear at an early age (even a child may be subject to the complaint), but they occur especially in persons of more advanced years, in this case in those approximately between the ages of 40 and 60. Obviously the line cannot be drawn more narrowly concerning a chronic complaint such as gallstones. Therefore the age limits given here are intentionally relatively wide.

The incidence of gallstones according to age is found to differ as regards sex. Stones appear to occur in men only sporadically before the age of 50 years; they develop as a rule between the ages of 60 and 65 and up to 85 and 90. One finds, further, that the relative increase of observed incidence as against the calculated average incidence increases progressively, so that at the period between 75 and 79 it is 60 per cent, between 80 and 84, 75 per cent, and between 85 and 89, 100 per cent. After the ages of 85 to 89, the relative increase diminishes. From this it would seem that new stones may continue to appear at least up to the age of 85. In other words, one might say that in men new stones can form at least up to the age of from 80 to 85 years. In women the first small increase in incidence occurs between the ages of 25 and 35 years, and the second, between the ages of 45 and 55. Probably these increases are associated with the first pregnancy and with the climacteric. That there is no increase in men within those age periods argues in favor of this assertion. Strictly speaking, stones seem to make their real appearance in women between 50 and 55 and between 80 and 85 years. At these ages incidence curves in clinical cases may be seen to exceed the calculated average curves. The relative increase as against the calculated average in women goes on to from 80 to 84 years, when it is 37 per cent. Judging from this, it would seem that in women gallstones can form at least up to 75 and 80 years of age.

INCIDENCE VARIATION DURING DIFFERENT PERIODS

It has been seen from table 1 that the incidence of gallstones varies during the years. In reference to a complaint such as gallstones, in which stones have been known to lie ten years or more in the gallbladder without causing death or giving rise to a symptom which compelled the patient to go to a hospital, one is obviously unable to pay attention to the separate yearly variations but must take longer periods into consideration. I have chosen periods of three years, fully aware that the time is short, but this choice is due to the fact that this investigation comprises only a period of ten years. An illustration of the results of this investigation is shown in chart 2.

From this chart it may be seen that there has been a steady increase in the incidence of gallstones in women and men during the last ten years in Stockholm. In order to illustrate still further how the complaint varies in its incidence in a decided manner during certain periods, I have included in chart 2 the incidence curves in postmortem material from Rostock, Germany, during the years 1911 to 1925.[1]

A study of this material shows how during the years of the World War and the following years, to the close of 1922, the incidence diminished, especially in women. To what this is due it is impossible to say definitely, as the report lacks a statement as to the total age and sex incidence during the period in question. It is conceivable, however, that during these years there occurred a general decrease in the average age

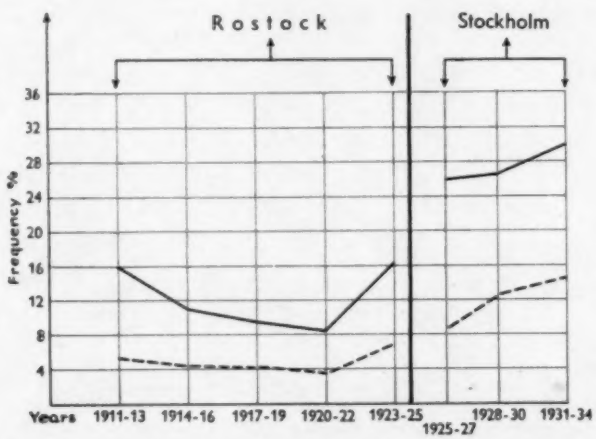

Chart 2.—The frequency of biliary calculus in Rostock, Germany, and Stockholm, Sweden, during the years 1911-1934.

of patients who came to autopsy, and as stones belong more especially to age than to youth, a natural explanation may be found here for the diminution in question. It would seem reasonable that the decrease in age of patients who came to autopsy should have been manifested equally in the sexes, or rather more in men, which was not the case. It is not unlikely, moreover, that the decrease was due to impaired nutrition during these years of dearth, when one considers the existence of a definite correlation between lipomatosis and certain types of stones (tables 5 and 6). This is further supported by the fact that the decrease occurred mostly in women, when it is remembered that it is especially

1. Schretzenmayr, Annemaria: Gallensteinleiden und Konstitution, Ztschr. f. Konstitutionslehre **13**:792, 1928.

women in a position to enjoy nutritious food who are liable to have lipomatosis.

DISTRIBUTION OF GALLSTONES IN SWEDEN

When one knows that the incidence of a certain disease, and perhaps of gallstones in particular, at a certain hospital depends on a number of factors, including the correctness of the diagnosis, the surgeon's repute and the mentality of the inhabitants of the neighborhood (as to whether they often seek medical advice or not), there are possibilities that the result of this investigation may not exactly correspond with the real state of affairs. On the other hand, I feel obliged to avail myself of these annual reports from the public hospitals, as they afford the only material on which to base a study.

TABLE 4.—*Distribution of Stones According to Sex and Type*

Type of Stone*	P.		Ch.		P-Ch.		P-C.		P-Ch-C.	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Solitary	15	12	43	13	13	5	12	12	43	8
1 group	76	56	2	..	24	3	68	24	85	27
2 groups	8	8	1	..	6	1	29	19	54	19
3 groups	2	1	..	..	3	..	4	4	10	7
4 groups	..	..	..	..	..	..	..	..	2	..
Gravel	3	1	..	..	..	..	2	..	..	..
Enclosed stone	1	1	1	2	..	..	..	2	6	4
Total	104 (57%)	78 (43%)	46 (78%)	13	46 (83%)	9	115 (66%)	59	194 (76%)	61
	182 (25%)		59 (8%)		55 (7½%)		174 (24%)		255 (35%)	

Enclosed stone in 47 cases, i. e., 2.34% of the total cases of gallstones

* P. indicates a pure pigment stone; Ch., a pure cholesterol stone; P-Ch., a mixed pigment and cholesterol stone; P-C., a mixed pigment and calcium stone, and P-Ch-C., mixed pigment-cholesterol-calcium stone.

It is evident from chart 3 that stones occur on the whole more frequently in South Sweden (Svealand and Götaland) than in North Sweden (Norrland). Norrland is mostly a mountainous district, while Svealand and Götaland consist mostly of fertile, lowland tracts. Also it will be seen that the incidence is especially great in the neighborhood of Örebro (a relatively rich town on a fertile plain in Svealand) and on the fertile plain of Östergötland (South Sweden), while it is obviously inconsiderable on the rocky moorland districts of Småland and the Västgöta heath. One finds the lowest incidence in the fishing villages of Bohuslän and Blekinge (South Sweden) and in the barren districts of Kolmården, Bergslagen and Norrbotten (North Sweden). It would thus seem as if cases of gallstones are more numerous in rich and fertile districts and of rarer occurrence in poorer and more barren areas.

TABLE 5.—*Diseases and Changes with Observed and Actual Correlation with Gallstone*

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Disease	Incidence			Combined with Gallstone								
				Observed			Calculated Actual Correlation*					
							Females		Males		Total	
	Females	Males	Total	Females	Males	Total	No.	%	No.	%	No.	%
Cholecystitis, acute	...	...	71	10	13	23	.....	....	.....	....	9 ± 3	9
Cholecystitis, chronic	253	159	412	222	123	345	154 ± 7	58.1	104 ± 4	62.9	264 ± 8	62
Disturbances in flow of bile	114	60	174	91	30	121	61 ± 5	49.1	23 ± 2	35.0	87 ± 5	47
Cancer of gallbladder	30	6	36	22	1	23	14 ± 2	40.0	0	....	16 ± 2	39
Cancer of bile ducts	15	11	26	8	1	9	4 ± 1	20.0	0	....	4 ± 2	8
Lipoidosis vesesica fellea	101	60	161	15	7	22	.....	....	.....	....	.....	..
Cirrhosis of the liver	105	252	357	34	48	82	6 ± 4	1.9	18 ± 5	5.2	12 ± 7	1
Furrowed liver	248	...	248	59	...	59	.....	....	.....	....	.....	..
Tumor, principally cancer of pancreas	41	25	66	14	3	17	3 ± 3	....	.....	....	4 ± 3	..
Cancer of head of the pancreas	24	11	35	8	1	9	2 ± 2	....	.....	....	2 ± 2	..
Enteritis; enterocolitis	...	...	101	15	3	18	.....	....	.....	....	.....	..
Pneumonia	430	378	808	318	187	505	202 ± 9	44.9	142 ± 6	36.0	347 ± 11	42
Hyperplasia lienica	1,021	1,014	2,035	271	165	436	.....	....	43 ± 9	3.3	37 ± 15	1
Lipomatosis universalis	330	141	471	143	36	179	54 ± 8	18.9	19 ± 4	10.6	87 ± 8	17
Lipomatosis pancreatica	370	273	643	128	63	191	91 ± 8	22.4	30 ± 5	9.2	126 ± 10	18
Lipomatosis hepatica	...	...	421	38	22	60	.....	....	.....	....	.....	..
Diabetes mellitus	132	85	217	53	25	78	17 ± 5	9.1	15 ± 3	14.1	36 ± 6	14
Xanthomatosis mesenterii	7	9	16	3	3	6	1 ± 1	....	2 ± 1	11.1	3 ± 1	13
Lipoidosis adrenalis	161	128	290	58	34	92	15 ± 5	6.2	18 ± 4	10.2	33 ± 7	9
Cancer	...	...	1,239	154	64	218	.....	....	.....	....	.....	..
Cardio-arteriosclerosis	...	...	6,031	753	297	1,050	.....	....	.....	....	.....	..
Tuberculosis, acute progressive	...	...	1,947	66	49	117	.....	....	.....	....	.....	..
Tuberculosis, healed and chronic induration	548	853	1,401	248	112	391	100 ± 9	16.6	12 ± 8	0.5	116 ± 13	7
Tuberculous calcification	...	...	359	106	37	143	.....	....	.....	....	73 ± 7	18
Calcification (tuberculous excepted)	345	137	482	107	58	165	14 ± 8	1.8	42 ± 4	27.7	71 ± 8	13
Osteoporosis	223	46	269	53	5	58	.....	....	.....	....	.....	..
Pernicious anemia	36	19	55	22	8	30	13 ± 3	28.0	6 ± 1	26.3	19 ± 3	29
Anemia universalis	...	...	126	15	14	29	.....	....	.....	....	4 ± 4	..
Hemosiderosis of the liver	32	47	79	18	16	34	10 ± 2	25.0	10 ± 2	17.0	19 ± 3	20
Stasis of portal vein	...	...	1,668	...	...	511	.....	....	.....	....	229 ± 14	13
Stasis of the liver	...	...	1,184	242	109	351	.....	....	.....	....	119 ± 12	9
Fibrosis testis	...	230	230	...	46	46	.....	....	19 ± 5	6.1	19 ± 5	6
Hypertrophia prostatae	...	682	682	...	130	130	.....	....	49 ± 7	6.2	49 ± 7	6
Struma colloides (adenomatosa)	210	38	248	68	8	76	11 ± 6	2.4	4 ± 2	5.3	27 ± 6	9
Cysta ovarii	300	...	300	49	...	49	.....	....	.....	....	.....	..
Tumor uteri (benign)	...	...	1,186	297	...	297	.....	....	.....	....	.....	..
Diverticulum of intestine (except juxtapapillare)	62	25	87	20	5	25	3 ± 3	....	2 ± 2	....	8 ± 4	..
Diverticulum juxtapapillare	58	36	94	27	13	40	11 ± 3	13.8	9 ± 2	19.4	22 ± 4	19.1
Hernia	...	...	195	2	16	18	.....	....	.....	....	.....	..
Malformations	516	401	917	144	54	198	5 ± 9	....	6 ± 6	....	18 ± 11	..

* In the column "Calculated Actual Correlation," a minus sign has been used in those instances in which the correlation was negative. The correlation was positive but not statistically sure ($3 \times \xi$ are not $>$ the calculated correlation) in the following conditions: acute cholecystitis, cirrhosis of the liver (females), lipoidosis adrenalis (females), tuberculosis, healed and chronic induration (male), calcifications, tuberculosis excepted (females), and struma colloides adenomatosa (males).

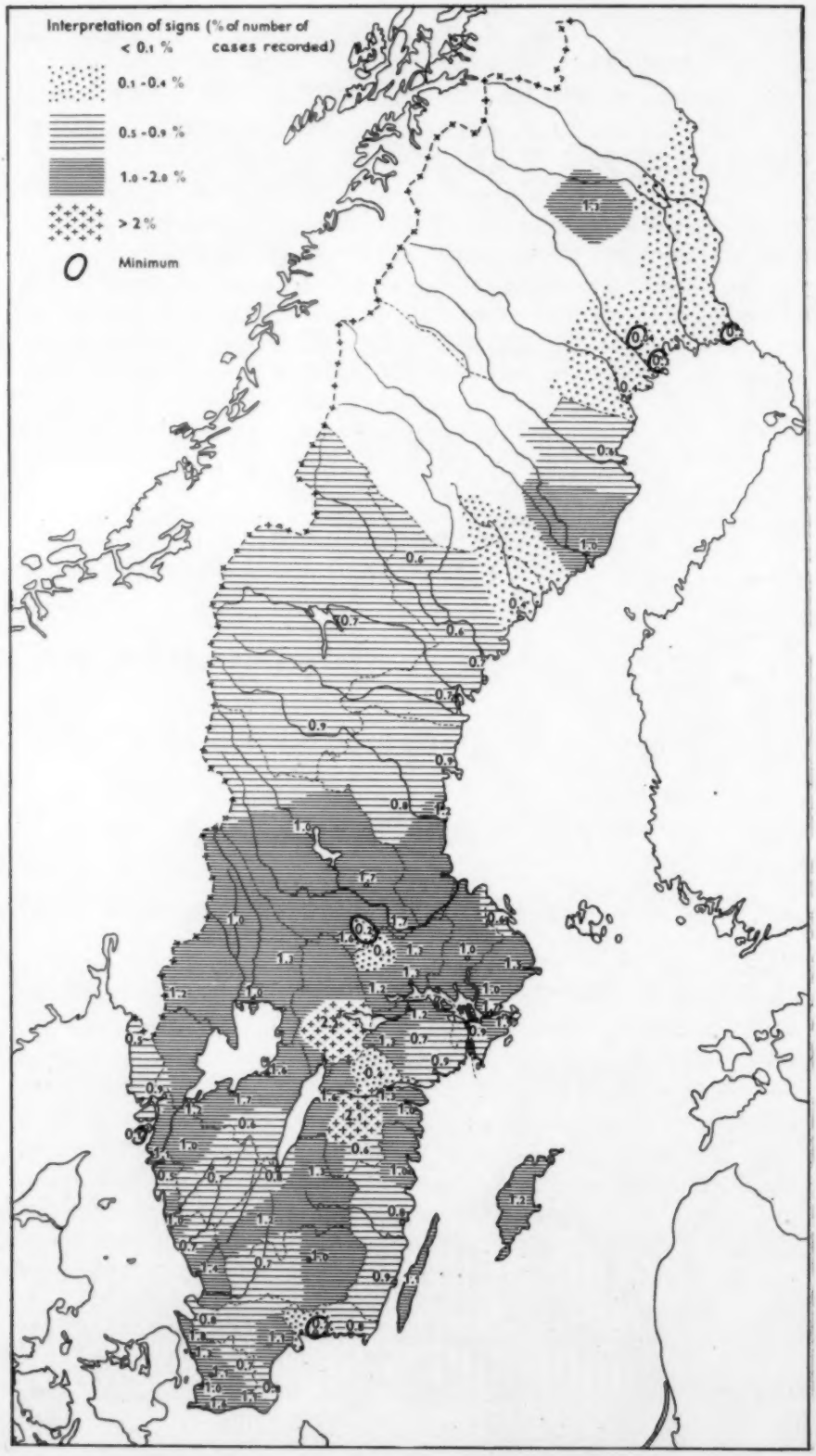

Chart 3.—The distribution of gallstones in Sweden.

DISTRIBUTION OF THE VARIOUS TYPES OF STONES

The distribution of the stones according to sex and type is given in table 4.

Of the various types of stone, the mixed pigment-cholesterol-calcium stone is the most common. This type was present in about one third of the whole group of material. The pure pigment stone and the mixed pigment and calcium stone comprised each about one fourth of the group, while those of rarest occurrence, the pure cholesterol stone and the mixed pigment and cholesterol stone, comprised about one twelfth of the whole.

TABLE 6.—*Distribution of Stones According to Disease*

	Pigment Stones				Cholesterol Stones				Calcium Stones				
	Pure		All Stones		Pure		All Stones		P-C.		P-Ch-C.		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	Total No.
Normal	182	25.1	666	91.9	59	8.1	369	50.9	174	20.0	225	35.2	725
Cholecystitis, acute	1	....	6	....	1	14.3	5	71.4	1	....	4	57.1	7
Cholecystitis, chronic	24	....	153	....	17	10.0	99	58.2	47	27.6	72	42.4	170
Disturbances in motility of bile ducts	18	29.0	54	....	8	12.9	31	....	13	....	17	....	62
Cancer of gallbladder	1	....	9	....	2	18.2	8	72.7	2	....	5	45.5	11
Cancer of bile ducts	0	....	3	....	1	25.0	4	100.0	0	....	2	50.0	4
Cirrhosis of liver	28	35.9	72	92.3	6	....	37	....	13	....	30	38.5	78
Hemosiderosis of liver	10	62.5	16	100.0	0	....	1	....	5	31.3	0	....	16
Pernicious anemia	10	55.6	18	100.0	0	....	4	....	4	....	4	....	18
Lipomatosis universalis	19	....	97	....	12	11.0	59	54.1	31	28.4	34	....	109
Lipomatosis pancreatica	6	....	51	....	8	13.6	47	79.7	6	....	37	62.7	59
Diabetes mellitus	10	....	39	92.9	3	....	22	52.4	10	....	14	....	42
Xanthomatosis, mesenteric	3	60.0	5	100.0	0	....	1	....	1	....	1	....	5
Lipoidosis adrenalis	15	....	51	....	7	12.1	25	....	18	31.0	16	....	58
Tuberculosis, healed	62	....	223	92.9	17	....	118	....	60	25.0	80	....	240
Tuberculous calcification	23	....	106	96.4	4	....	47	....	40	36.4	34	....	110
Calcification	48	....	190	96.4	7	....	84	....	65	33.0	56	....	197
Fibrosis testis	10	43.3	20	....	3	13.0	10	....	3	....	5	....	23
Hypertrophia prostatae	30	43.2	65	....	6	....	23	....	18	25.4	14	....	71
Struma colloides	10	....	48	96.0	2	....	29	58.0	11	....	17	....	50
Diverticulum juxtapapillare	14	40.0	9	....	1	10.0	5	....	1	....	2	....	10
Pneumonia	48	36.9	126	96.9	4	....	63	....	19	....	57	43.9	130

Distribution according to sex indicates that on the basis of percentage, and also absolutely, the pure pigment stone is the most common in men while the pure cholesterol stone and the mixed pigment and cholesterol stone, according to percentage, are most common in women.

In addition to the existing differences between the pure cholesterol stone and the pigment stone, still another difference comes to light when one investigates the distribution of stones in regard to size. Pigment stones appear multiply as a rule and are variable in size, while pure cholesterol stones generally occur singly. Nevertheless, as table 4 indicates, pure cholesterol stones in a few cases have even appeared in

variable size, a coincidence of special interest when one remembers statements as to the metamorphosis of gallstones through special cholesterol processes, as set forth in the literature. Meckel von Hemsbach seems to have been the first to have made this observation. Later Boysen [2] and Naunyn [3] investigated further and proved the correctness of these observations. The metamorphosis [4] implies that a quantity of already formed pigment-calcareous concrement collects dissolved cholesterol if allowed to remain in the gallbladder and bile ducts any length of time. The dissolved cholesterol (the presence of bile acids is necessary to dissolve the cholesterol) expels the calcium, which, by means of the weak acids, is brought into a dissolved condition. By this process the cholesterol is separated and precipitates into its colloid form, which later, according to Ostwald's *Reifungsprinzip,* becomes crystallized and is known as typical cholesterol crystals. Thus it is seen how certain pigment-calcium stones can be entirely transformed into pure cholesterol stones. However, according to Naunyn, a distinction must be made between cholesterol stones thus formed and the so-called primary crystalline cholesterol stones, which, it would seem, are formed from a primary nucleus of crystalline cholesterol and, in distinction from the cholesterol stones, have a nucleus clearly defined from its surroundings. This observation is made in order to explain that not all pure cholesterol stones (according to present knowledge) develop from mixed pigment and calcium stones and, in addition, to explain that the following argument must be confined to certain pure cholesterol stones.

In consideration of this metamorphosis, one is tempted to believe that pure cholesterol stones, in some cases, appear in variable size as remains from the time when they already existed as mixed pigment and calcium stones. In other words, it would imply that some, at least, of the pure cholesterol stones were mixed pigment and calcium stones of years' standing.

DISEASES AND PATHOLOGIC CHANGES WHICH HAVE ACTUAL CORRELATION WITH GALLSTONES

To determine which diseases have an actual correlation with gallstones I have made note of the diseases and pathologic changes which, when investigating postmortem material, I found combined with stones;

2. Boysen, J.: Ueber die Struktur und die Pathogenese der Gallensteine, Berlin, S. Karger, 1909.

3. Naunyn, B.: Die Gallensteine, ihre Entstehung und ihr Bau, Jena, Gustav Fischer, 1921.

4. Naunyn,[3] p. 23.

also, I have ascertained the number of diseases and to what extent they were found in connection with gallstones. In addition, I have statistically calculated how many chance combinations might conceivably appear (i. e., assuming no existing correlation between gallstones and the disease in question). By subtracting the number of chance combinations from the number of observed combinations and by calculating and making due allowance for the average miscalculation, I have succeeded in obtaining the figures for an actual correlation. The results are shown in table 5.

Cholecystitis, Especially the Chronic Type (in Approximately 60 Per Cent of the Cases).—It is not possible to determine from these statistics whether cholecystitis may be considered primary or secondary to gallstones. Clinical experience teaches, of course, that symptoms of cholecystitis appear after signs that a stone has become lodged, i. e., after the stone already exists. The report on clinical symptoms (table 3) argues in favor of this, and so, to some extent, does the correlation between the various diseases and the different types of stones (table 6), which indicates that it is especially the larger (older) types (pure cholesterol stones, mixed pigment and calcium stones and mixed pigment-cholesterol-calcium stones) which manifest decided correlation with cholecystitis. That it is mainly chronic cholecystitis which occurs in this association with gallstones may be assumed to be due to the irritation caused by the stones in the bladder maintaining an inflamed condition, which becomes chronic. Against the theory that infection should be a primary factor in the formation of stones there are reported in the literature cases of infection of the gallbladder, cholecystitis and disturbances in the motility of the bile of many years' standing without the formation of stones.[5] But, as previously mentioned, it is impossible to make any definite statement.

Disturbances in Motility in the Biliary Ducts (in Approximately 50 Per Cent of the Cases).—It is not possible here to regard a priori those disturbances in the motility of gall as primary to the formation of stones. It is true that in most of the literature stress is laid on the theory that such a disturbance disposes to the formation of gallstones, but I have nowhere found evidence to support this assertion. Should one assume a disturbance in motility to be primary, a decided correlation will be seen between severe sclerosis of the head of the pancreas or other processes there, which deform the ductus choledochus and thus hinder the normal emptying of bile. No such correlation is indicated, however, throughout this relatively large amount of material. It is not

5. Törnqvist, G. W.: Beiträge zur Pathologie und Therapie der Gallensteinkrankheit, Stockholm, P. A. Norstedt & Söner, 1903, pp. 21-22.

out of the way to believe that stones, through mechanical irritation or indirectly through inflammation, give rise to cicatrization and strictures in the biliary ducts, with the attendant hindrance to the emptying of bile. Only incontestable experiments, however, can solve the problem as to the correlation between a disturbance in motility in the biliary ducts and the formation of gallstones. Such experiments have been made, but up to the present, as far as I know, have not given positive results.

Tumors, Especially Cancer in the Gallbladder and Bile Ducts (in Approximately 40 and 8 Per Cent of the Cases, Respectively).—These conditions will be considered later in connection with their correlation with the various types of stones.

Certain Disturbances in the Metabolism.—The following disturbances in metabolism were encountered: (*a*) lipomatosis universalis (in approximately 17 per cent of the cases and lipomatosis pancreatica (in 18 per cent of the cases); (*b*) diabetes mellitus (in approximately 14 per cent of the cases); (*c*) lipoidosis adrenalis (in approximately 9 per cent of the cases); (*d*) xanthomatosis mesenterii, of which there were only sixteen cases included in the whole of the material, consequently the calculation of correlation will be uncertain.

With certain reservation for diabetes, it might in all probability be considered unlikely that these disturbances of metabolism are due to gallstones or any of the complications, but it is likely enough that these, or other factors connected with their appearance, occurrence or disappearance, favor the origin or further formation of stones. I shall return to this factor when dealing with the types of stones having a correlation with lipomatosis.

Calcification of Different Kinds, Especially Tuberculous Calcification (in Approximately from 15 to 20 Per Cent of Cases) and Healed Tuberculosis (in 7 Per Cent of the Cases).—It is already known that healed tuberculosis is combined with gallstones more often than active or acute tuberculosis. From this it has been understood that tuberculosis in a case of gallstones more often takes on a mitigated form and evinces a greater tendency toward healing than when gallstones are not present.[6] This conclusion is, however, not quite correct, because, as will be shown later, the correlation applies not to gallstones in general but only to certain types (table 6). This report also indicates that it is especially the tuberculous calcification which has a correlation with gallstones, and when one sees, further, that pathologic calcification as a rule manifests almost as great a correlation with gallstones, the explanation might

6. Boysen,[2] p. 795.

assumably be that it is the tendency to calcific precipitation in the various pathologic processes which brings about the correlation.

Pernicious Anemia and Hemosiderosis of the Liver (in Approximately 29 and 20 Per Cent of the Cases, Respectively).—Table 5 illustrates how a calculated correlation occurs between pernicious anemia and gallstones in sixteen cases. A similar illustration is given of sixteen cases of hemosiderosis of the liver and gallstones. There were sixteen cases of pernicious anemia and hemosiderosis of the liver in the material. It may, of course, be incidental that the figures in these cases coincide. It is conceivable also that in those cases in which pernicious anemia manifests a pathologico-anatomic hemosiderosis of the liver, the possibility of or disposition to formation of gallstones is great. It is of special interest, and an account of the same will be given later, that hemosiderosis of the liver in just sixteen cases, i. e., the total number of cases, shows a decided correlation with a certain type of stone. This repudiates the idea that the report previously cited may be a coincidence.

Stasis of the Liver and of the Portal Vein (in Approximately 9 and 13 Per Cent of the Cases, Respectively).—An explanation of the correlation between these complaints and gallstones can obviously not be speculated on without experiments. As earlier experiments seem to indicate that the formation of a concretion is dependent on a change in the p_H of the bile,[7] it should not be considered out of place to ask whether a local stasis can change the p_H of the bile.

Cirrhosis of the Liver (in Approximately 1 Per Cent of the Cases), Fibrosis Testis (in Approximately 6 Per Cent) and Hypertrophia Prostatae (in Approximately 6 Per Cent).—At first sight, undoubtedly, it would appear somewhat unreasonable to assume the existence of a correlation between fibrosis testis and hypertrophia prostatae, respectively, and gallstones. But Henschen and Bruce [8] have drawn attention to a certain parallelism in the appearance of cirrhosis of the liver and fibrosis testis. In addition, as cirrhosis of the liver in men (5 per cent) and fibrosis testis show practically the same correlation with gallstones in this material (13 and 14 per cent, respectively), the correlation with gallstones must obviously be due either to some possible common cause or to the parallel diseases, cirrhosis of the liver and fibrosis testis or to cirrhosis of the liver alone. From the report on the correlation of these

7. Hanser, Rob: Gallensteinkrankheit, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1929, Berlin, Julius Springer, vol. 5, no. 2, p. 801.

8. Henschen, F., and Bruce, T.: Ueber die Häufigkeit und Formen der Lebercirrhose in Stockholm, Compt. rend. première conf. internat. de path. géog. **1**:249, 1931.

diseases to certain types of stones (see table 6), it may be gathered that both diseases show a decided and similar correlation with a certain type of stone. This correlation speaks for a common factor in the formation of stones.

Pneumonia (in Over 40 Per Cent of the Cases).—This condition has shown a decided and great correlation with gallstones. It is well to adopt a skeptical attitude, however, in this connection, as pneumonia is one of the commonest immediate causes of death, and when studying the reports it is difficult in some cases to discriminate; therefore, statistical calculations, to some extent, are unavoidably misleading. In only those cases in which at autopsy lumps of pigment were found, which to all appearances were formed shortly before death, was pneumonia included. Thus the correlation (according to table 6) between pneumonia and pigment stones may be misleading.

Struma Colloides (Adenomatosa) (in Approximately 8 Per Cent of the Cases).—It is remarkable how frequently at autopsy struma colloides and adiposity have been found synchronously. I cannot, of course, assert that this particular adiposity was responsible for the correlation, but I am inclined to believe that such is the case. According to the modern endocrinologic theory that a colloidal hypertrophic struma is the outcome of hypofunction of the thyroid gland, slow combustion in the body with a tendency to adiposity might be assumed. When it is understood that a decided correlation exists between pathologic adiposity and gallstones, a feasible explanation should be found as to the correlation between colloidal struma and gallstones, and in these cases the simultaneous and relatively frequent lipomatosis.

CORRELATION OF VARIOUS DISEASES AND PATHOLOGIC CHANGES WITH THE DIFFERENT TYPES OF STONE

It is stated that diseases and pathologic changes showing decided correlation with gallstones also have a decided correlation with a certain type of stone (table 6).

I shall touch on only the most important results of my investigation. These show the diseases and pathologic changes which manifest a calculated absolute correlation with certain types of gallstones.

1. Pure pigment stones were found associated with pernicious anemia, hemosiderosis of the liver, cirrhosis of the liver, fibrosis testis and hypertrophia prostatae.

Since fibrosis testis, hypertrophia prostatae and cirrhosis of the liver are diseases which appear mostly in men, their absolute correlation with pure pigment stones should afford an explanation as to why this type of stone is found (on the basis of percentage) more generally in men than in women (table 4).

As far as pernicious anemia and hemosiderosis of the liver are concerned, reasoning in connection with their relationship to gallstones has led one to believe that in all probability it is only in cases in which pernicious anemia gives rise to hemosiderosis of the liver that the disposition to gallstones arises. Thus, it can be said that hemosiderosis of the liver is the deciding factor for a disposition toward the formation of stones. When it is seen that pigment stones appear in every case of hemosiderosis of the liver (table 6) and that in a vast number of cases (62.5 per cent) these are pure pigment stones, one has every reason to believe that it is the excess of pigment in the liver indicated by hemosiderosis which is responsible for the disposition to stone formation.

2. Pure cholesterol stones were found associated with cancer of the gallbladder and bile ducts—lipomatosis and lipoidosis in the kidneys.

Owing to the understanding that it is the pure cholesterol stone which lies the longest in the bladder, an assumption should not be out of place that by reason of the constant irritation which goes on it has every possibility of giving rise to a cancerous degeneration of the mucous membrane of the gallbladder. Furthermore, when cancer is found situated where there has been the most irritation in walking and standing positions, i. e., the fundus, it would seem most likely that cancer of the bile ducts and gallbladder is secondary to stone and that the explanation of the absolute correlation to pure cholesterol stone is to be sought here.

That correlation exists between lipomatosis and gallstones is already proved and in various ways, as also is the assumption that this correlation should refer to the cholesterol stones mentioned by Naunyn,[3] Aschoff [9] and others. This investigation not only indicates the existence of decided correlation between lipomatosis and cholesterol stones, but also points out the nonexistence of a correlation between lipomatosis and pigment stones (see table 6, "All Stones"). How is this correlation to be interpreted? There are statements in the literature (McNee, Bacmeister and Landau) to the effect that a food rich in cholesterol might to some extent increase the percentage of cholesterol in the bile by cholesteremia [10] and, further, that such an increase is likely to bring in its train cholesterol or pigment-calcium stones which may be in the bladder already or eventually precipitate cholesterol crystals, thereby constituting the first predisposition toward a primary crystalline cholesterol stone.[9a] Should this assumption be correct, one has an obvious expla-

9. (*a*) Aschoff, L.: Von den Bedingungen der Gallensteinbildungen, Deutsche med. Wchnschr. **52**:1755 and 1799, 1926. (*b*) Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909.

10. Boysen,[2] p. 793.

nation of the connection existing between lipomatosis and pure cholesterol stones.

3. Pigment calculi were found in association with calcifications of various kinds, especially tuberculous calcification and perhaps healed tuberculosis.

In considering the correlation of these diseases, or rather, these conditions with gallstones (table 5), one comes to the conclusion that the correlation was due to the tendency toward calcification in pathologic processes which existed previous to these conditions. When it is seen that the correlation refers to the calcareous stones, it is not difficult to assume that in connection with these conditions the percentage of calcium in the bile increases and a tendency to calcification of the foreign substances found there arises. This is only an assumption, however. It has been proved experimentally that the calcium in the bile does not increase if the percentage of calcium in food is augmented. This cannot be said in any way to interfere with the foregoing hypothesis, as in the present case reference is made to the metabolism of calcium in connection with pathologic conditions.

4. The mixed pigment-cholesterol-calcium stones were found primarily in association with chronic cholecystitis.

In a case of prolonged chronic cholecystitis, increased quantities of albumin appear in the bile, and considering that albumin is one of the most important coagulating factors in connection with the formation of stone, the possibilities of a combination of the various substances forming a pigment-cholesterol-calcium stone are not far to seek.

SUMMARY

Gallstones, a common complaint, occurs in Stockholm in approximately one tenth of the inhabitants. The incidence in Sweden varies, however, according to the location. Stones appear to occur more frequently in rich and fertile districts and are of rarer occurrence in poorer and more barren areas. The incidence varies also according to time and seems to be less frequent during years of famine and the years immediately following than in times of plenty.

Only a fractional number of the patients (in this case, one fourth) have clinical symptoms of gallstones. But making reservation for miscalculations, due to the method of investigation, concerning what one would wish to consider the conspicuous results of one's investigation, it would seem that as soon as symptoms in the form of "typical painful attacks" appear, the risk of later complications, such as cholecystitis and cholangeitis, is very great, especially in the case of repeated attacks.

Certain diseases and pathologic changes show a decided correlation with gallstones. This correlation refers only to certain types of stones;

consequently, cirrhosis and especially hemosiderosis of the liver, i. e., processes which accompany the accumulation of pigment in the liver, show an actual correlation with pigment stones, especially those which are of the pure type. Lipomatosis shows an actual correlation with pure cholesterol stones; calcification, especially tuberculous calcification, i. e., when there is a tendency to calcification in pathologic processes, shows an actual correlation with pigment calculi; and, lastly, cholecystitis —especially the chronic form, i. e., a process which augments the albumin of the bile, its most important coagulating factor—shows an actual correlation with the mixed pigment-cholesterol-calcium stones.

CHONDROMATOSIS OF THE JOINTS

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Despite the great number of articles on chondromatosis of the joints which have appeared since Reichel's publication in 1900, the condition has remained an interesting problem which by no means is entirely solved. From a review of the literature one gets the impression that the diagnosis, which is very simple when the condition is outspoken, is made too often and that many conditions which belong to the group of hypertrophic arthritis are diagnosed as chondromatosis because of the presence of a great number of joint bodies. Chondromatosis of the joints is a rare condition. Only three cases were found in the extremely rich material of the orthopedic department of the State University of Iowa. A diagnosis of chondromatosis was made many times, but the diagnosis did not withstand a more critical analysis. Three cases are reported here which were interesting from a clinical and a pathologic point of view.

REPORT OF CASES

CASE 1.—A man aged 29 complained of limitation of motion in the left shoulder. He stated that nine years prior to admission to the hospital he was thrown from a horse. Shortly afterward his left arm began to atrophy, and he could lift it only a little. Within a year the power gradually returned, so that he was able to work again, but occasional pain and limitation of motion remained.

Physical examination showed that the left shoulder and arm were slightly atrophic. Motion was limited to 45 degrees of abduction, 40 degrees of external rotation and 45 degrees of flexion. The last degrees of motion were painful and seemed to be checked by a bony obstacle.

A roentgenogram (fig. 1*A*) showed that the inferior two thirds of the left shoulder was filled with numerous calcified round bodies, most of which were the size of a pea. The uniformity and the dense arrangement of the bodies gave a grapelike appearance. Two greater foci could be made out, a larger one situated more medially and a smaller one laterally, apparently along the long head of the biceps muscle in the intertubercular groove. The head of the humerus was misshapen and flattened, and there was some erosion of the bony joint surface. The joint space was slightly widened.

The diagnosis of chrondromatosis of the shoulder was made, and an open operation was performed. The joint capsule was found to be thickened. The entire joint space was filled with numerous small, free cartilaginous masses, ranging from 1 mm. to 1 cm. in diameter; some were smooth and shiny, and others were mulberry shaped. The head of the humerus and the glenoid fossa were covered with thin blue cartilage. All bodies which could be found, about 160, were removed, and the capsule was closed again.

The patient was reexamined one year and seven years after operation. The shoulder was well movable. There were some crepitation in the joint and some

atrophy of the deltoid muscle, but the patient had almost full use of the extremity and was well pleased with the result.

Of interest was the roentgenographic study. The picture (fig. 1 *B*) taken immediately after operation showed the number of calcified bodies to be greatly reduced. The lateral focus had been removed entirely, and medially there was still a good number of bodies present. A roentgenogram (fig. 1 *C*) made one year after operation showed that the number of bodies had further decreased. There was practically only one larger body present in the inferior portion of the joint and two smaller ones in the upper portion, which were not so densely calcified and apparently lay between the ends of the joint. The head of the humerus was markedly deformed and showed an uneven joint surface.

The histologic study revealed data of considerable theoretical significance. For this reason, an extensive pathologic report is given. A tag of synovial tissue (fig. 2) was examined which contained four more or less spherical cartilaginous

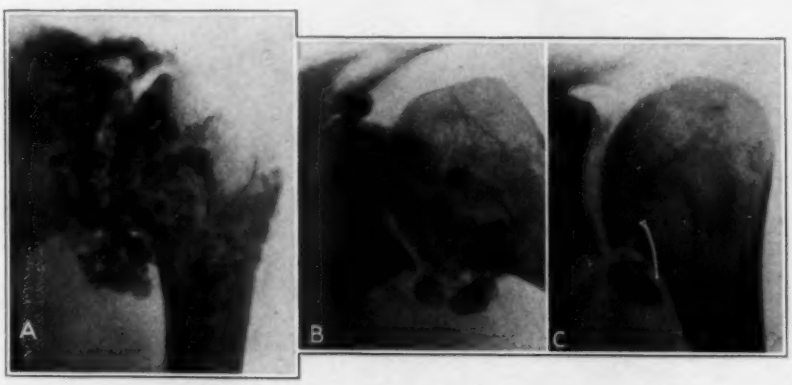

Fig. 1 (case 1).—Chondromatosis of the shoulder joint. *A* shows numerous calcified joint bodies filling the joint cavity and extending along the long head of the biceps in the intertubercular groove; *B*, the joint bodies remaining after operation; *C*, spontaneous resorption of joint bodies one year after operation. There is considerable deformity of the head of the humerus.

bodies. The density of the fibrous tissue of the tag varied, and there were a good many blood vessels. Synovial endothelium covered the smoother surfaces.

In the fibrous tissue there had occurred infiltration with a homogeneous reddish substance (fig. 3) which separated the collagenous fibers widely but did not interfere with their visualization. The cells, too, lay at greater distances from each other and assumed a spindle or stellate shape. In certain areas they had disappeared almost entirely, and then only a pinkish ground substance traversed by some fibers was to be seen. This represented the beginning of cartilaginification of fibrous tissue.

It was of interest to see that close to an area which had already become impregnated by ground substance, the connective tissue was similar to embryonal mesenchymatous tissue and contained small spindle-shaped and starlike cells, the fibrous meshwork being spread apart by edema. It is possible that the edema and the embryonal character of the connective tissue were preceding even the process of impregnation by cartilaginous ground substance.

In certain places and at the same time, but apparently independently of the process of cartilaginification, bone formation had taken place in the synovial fibrous tissue. The process of ossification was a primitive one, having as its basis fibrous tissue which became infiltrated by osteoid substance with the appearance of a greater number of cells, which in turn took over further bone apposition in form of osteoblasts. Calcification of the osteoid substance followed quickly.

Owing to the considerable proliferation of the young cartilaginous tissue, the focus had increased in size and showed, as it is characteristic for joint bodies, a certain tendency for concentric structure (fig. 4). This was seen especially well when there was calcification of the cartilage. Some of the small bodies were calcified almost in their entirety with dense precipitation of lime salts around the cartilaginous cells. The latter frequently disintegrated and even completely dis-

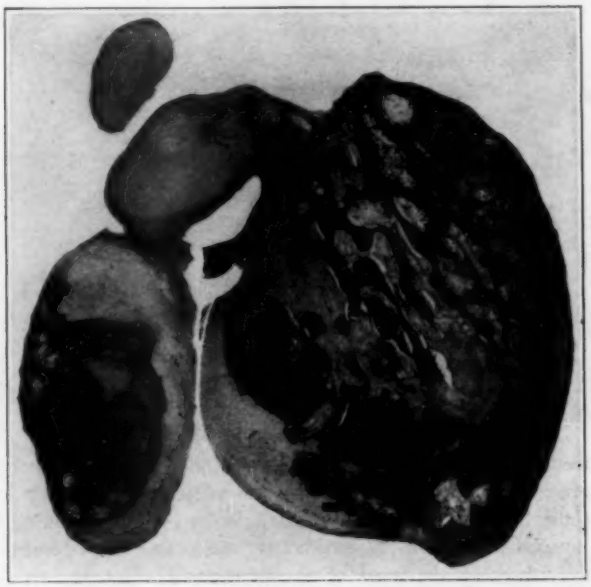

Fig. 2 (case 1).—Low power picture of a synovial tag containing four bodies, in part purely cartilaginous and in part osseous, with fibrous bone marrow. The bodies are united by strands of hyperemic synovial connective tissue.

appeared. When this ocurred the calcification was more homogeneous, involving ground substance and cell groups evenly. If, however, the calcification was not associated with necrosis of cartilaginous cells, later a secondary process of cartilage resorption took place owing to reactivation of the cartilage cells (fig. 5). This means that the cartilage cells included in calcified ground substance remained for some time in an active stage of low vitality. Later, for some unknown reason, they regained activity and, similar to the formation of Weichselbaum's lacunae in the joint cartilage, only with the difference that the latter develop in noncalcified cartilage, maintained a resorptive process which led to widening of the cell cavities by chondroclasia. Thus there appeared wide and lacunar cavities, separated from each other by irregular septums of calcified cartilaginous tissue

and filled by cartilaginous cells, which under proliferation showed a backward development toward fibroblasts.

More evident and easier to understand was the process of calcification along the periphery of the calcified joint bodies, where synovial fibrous tissue was preserved in the form of perichondrium. The superficial layers of this perichondrium, more exposed to traumatization during motion of the joint, were rather dense, with parallel concentric structure of the fibers. The deeper layers, protected from

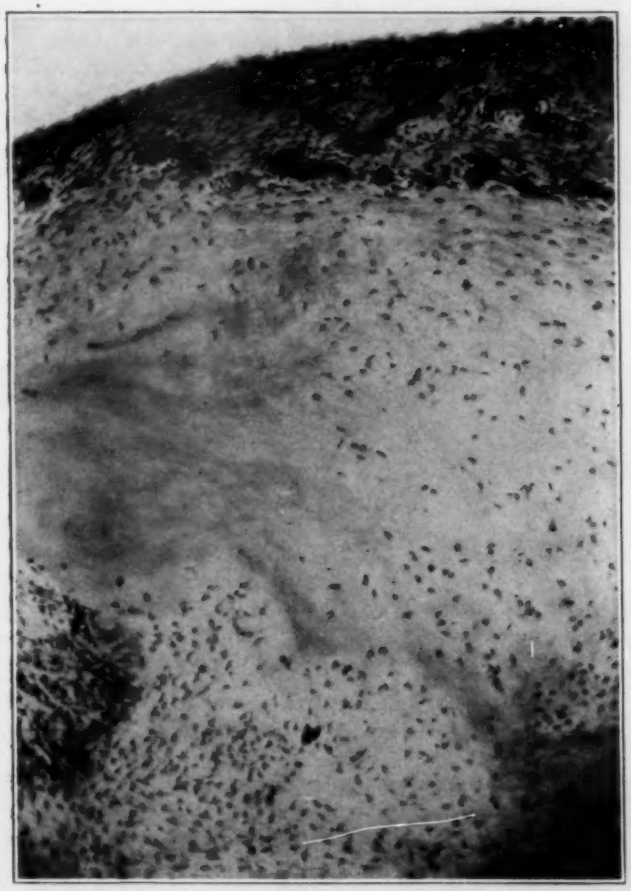

Fig. 3 (case 1).—Higher power photomicrograph than that in figure 2, showing the peripheral zone of one of the bodies. Diffuse impregnation of synovial fibrous tissue by primitive (eosinophilic) cartilaginous ground substance and rapid disappearance of cartilaginous cells are seen. Very cellular and well vascularized superficial layer of fibrous tissue is present—future perichondrium.

mechanical irritation, were loose and rich in cells and could be considered as a true cambium layer (figs. 4 and 5). This layer bordered on the calcified layer along a sharply lacunar line with mononucleated and multinucleated phagocytic elements in the lacunae. These cells were true chondroclasts, being derived from

the fibrocytes of the perichondrium and cambium layer. It could, however, also be seen that with this process of cartilage resorption, the cartilaginous cells up to now lying in calcified substance, as soon as they were freed changed to large fibrocytes, which participated in the composition of the cambium layer.

Blood vessels were not present over the lacunar area. It seemed that this process of decalcification was purely cellular or enzymatous and that a blood supply was not a prerequisite.

The largest of the joint bodies consisted of bony tissue to a considerable degree (fig. 2). The distribution of the different tissues was as follows: On the surface there was fibrous tissue in form of a perichondrium. Close to the surface there was noncalcified hyaline cartilage of not very high maturity. The cells were still spindle shaped, rarely spherical and without a tendency to group formation.

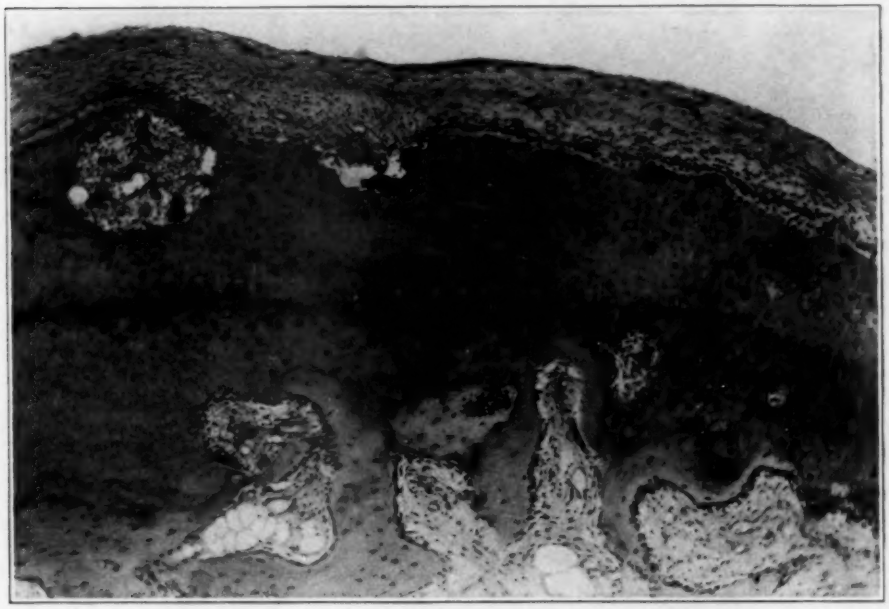

Fig. 4 (case 1).—Photomicrograph of the peripheral zone of a cartilaginous bony body, showing calcification of the superficial cartilaginous layer with definite concentric arrangement of increased zones of lime salt deposits; resorption of calcified cartilage from below and replacement by bony tissue; active osteoblastic bone apposition within the fibrous marrow spaces; resorption of calcified cartilage from above by multinucleated chondroclasts, and a fibrous tissue layer in the form of perichondrium on the surface.

As soon as calcification of the cartilage took place, the cells lay at greater distances from each other. They were more round and stood out more distinctly because of stronger calcification around the cells. The innermost portions of the body were made up of bony tissue. It was of interest to study the process of ossification.

The calcified cartilaginous tissue was often in intimate relation to the bony tissue. The most common form of osteogenesis was a primitive type of enchondral

ossification. Fibrous bone marrow with well vascularized processes invaded the calcified joint cartilage from below, which yielded under this vascular and chondroclastic resorption. On the lacunar surface of the calcified cartilage, bony tissue became apposed by osteoblasts, leading to the formation of primary spongy bone.

Enchondral ossification of this primitive type without any zone of cartilaginous proliferation was, however, not the only form of osteogenesis. It has already been mentioned that with synovial fibrous tissue as a basis, cartilaginous as

Fig. 5 (case 1).—Photomicrograph showing lacunar resorption of calcified cartilage by reactivation of the included cartilage cells. The freed cells form a part of the cambium layer of the perichondrium.

well as bony tissue may develop quite independently of each other at the same time in different places. The two tissues can merge, in which case a picture would result suggestive of direct metaplasia from cartilage into bony tissue. Such local connections of the two tissues are, however, not to be taken necessarily as genetic. They can be merely a topographic coincidence of the two tissues, which have developed independently in a common matrix of fibrous tissue.

As soon as bony trabeculae had formed, an active process of bone transformation could be observed. The irregular network of bony trabeculae was covered on its endosteal side by osteoblasts of almost epithelial connection, or, where bone absorption had taken place, with multinucleated osteoclasts in Howship's lacunae. With this process of bone transformation, the bone marrow also underwent changes. Fat cells appeared in the primarily well vascularized connective tissue, and one could see all the different stages from small lipoblasts with foamy protoplasm to large fat cells, which gradually occupied the entire marrow spaces.

The picture, in a general way, was that of rapid growth but also of rapid decline. The great amount of osteoclasts and chondroclasts made it easy to understand that joint bodies, as soon as calcification has taken place, may again disappear by cellular resorption. This fact explained also the peculiar finding that the synovial connective tissue between the cartilaginous bodies was extremely rich in

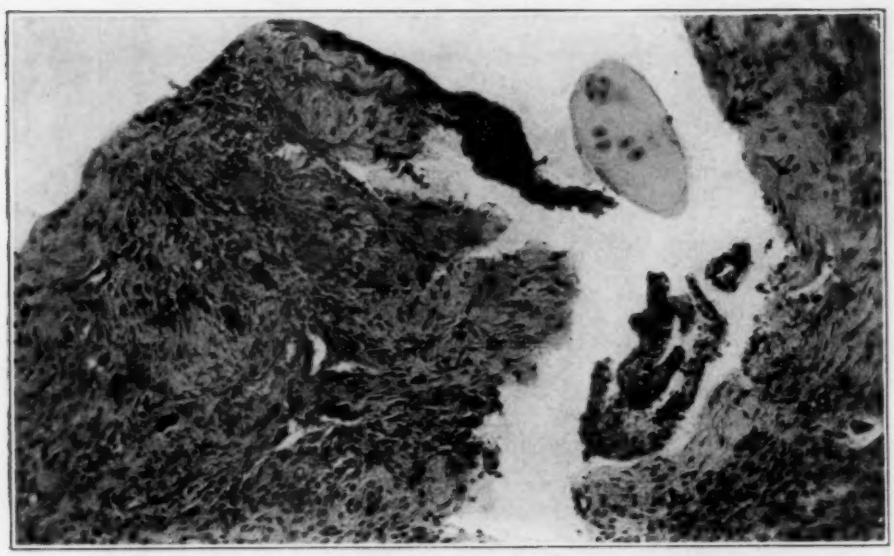

Fig. 6 (case 1).—Photomicrograph showing a strand of synovial tissue with many inclusions of small lacunar particles of calcified material (result of resorption of disintegrated calcified bodies) and a small island of mature hyaline cartilage attached to the synovia by fibrous tissue (appearing loose in the section).

small calcified fragments (fig. 6). They were lying included in the fibrous tissue without any reaction around them or were still undergoing disintegration by osteoclasts.

CASE 2.—A man aged 25 complained of pain and stiffness of the left hip joint. He was in excellent health up to four months before admission to the hospital, when he was suddenly seized by a sharp pain in the left hip while planting a garden. As he stooped over he felt something pop in his left hip, and since he could not straighten out he had to stay for a while bent forward; then he went down on his knees and spread his legs. This relieved the sharp pain. From this time on, the left hip remained in an abducted position. The patient had to go to bed because of the pain. The condition was diagnosed as rheumatism by a doctor. Heat

relieved the pain somewhat, but the most comfortable position was one of marked abduction and flexion of the leg. He was under the treatment of a chiropractor without effect.

On physical examination, the patient appeared to be in good health. He walked with marked abduction contracture of the left leg and was scarcely able to put weight on this extremity. The left hip joint was kept in a position of 30 degrees of flexion and 40 degrees of abduction. There was tilting of the pelvis upward and backward to compensate for the contracture and atrophy of the thigh of 3 inches (7.6 cm.). The region of the hip joint was not swollen or especially tender, and there was no local heat. From the contracted position of the joint, further abduction and flexion motion was free. Other motions could not be carried out, and any attempt to do so was extremely painful.

The roentgenograms (fig. 7) revealed considerable bony atrophy around the hip joint. The left femur was held in abduction of about 40 degrees. The head of the femur was well shaped but appeared to be pushed out from the socket so

Fig. 7 (case 2).—Roentgenogram of the left hip joint in marked abduction contracture. The head of the femur is subluxated and pushed out off the socket by an accumulation of noncalcified joint bodies in the lower portion of the hip joint.

that the joint space in the lower half was about twice as wide as that on the right normal side. The tear figure of the acetabulum was well developed. There was some obliquity of the roof, and the fossa acetabuli was definitely larger and slightly deeper than on the right side. The joint space in the upper portion of the joint was of normal width. There were no signs of arthritic erosion.

No definite diagnosis could be made. A tuberculous lesion of the hip had to be considered because of the strongly positive reactions to the cutaneous tests, but the patient's general health was good, and there had been no loss of weight and no fever. The widening of the joint space in the lower half suggested some soft tissues pushing the head gradually out, and an intra-articular new growth was considered. To arrive at a more conclusive diagnosis, biopsy was indicated.

The left hip joint was exposed through a Smith-Petersen incision. The joint capsule seemed to be thickened slightly on the anterior side, but this was considered as due to the flexion position of the joint, leading to some redundancy of the anterior joint capsule. The joint capsule was incised in the form of an H,

the cross-beam of which represented a longitudinal incision along the iliofemoral ligament, while one of the vertical portions of the H ran along the rim of the acetabulum, and the other around the neck of the femur. As soon as the capsule was incised, rather thick clear yellow synovial fluid escaped, carrying with it a few small cartilaginous bodies. More could be seen with further exposure of the joint. The bodies were purely cartilaginous and soft and varied in size from that of the head of a pin to that of a small pea. They were rarely truly spherical. When they were a little larger, they slightly resembled mulberries because of the presence of many small round prominences. The synovial membrane, as far as it could be seen from the incision, appeared to be of normal thickness. It was slightly hyperemic and extended from the neck of the femur toward the margin of the joint surface, here eroding, in an uneven way, the peripheral portions of the joint cartilage. The head of the femur was dislocated in the wound. The ligamentum teres was cut at its insertion to the fovea capitis. A peculiar picture presented itself at this area: The synovial cover of the fovea, extending then along the ligamentum teres, showed numerous small islands of cartilaginous tissue. The joint cartilage of the femur was slightly thinned out over the anterior portion, which had been out of contact with the acetabulum and probably under some pressure from the side of the joint capsule. The cartilage over this area was without its normal glistening appearance, thus revealing the first stage of degeneration. The insertion of the ligamentum teres together with the neighboring portions of the head were removed radically.

After complete dislocation of the head, the acetabulum was inspected. A startling picture was encountered. The entire acetabular cavity was densely filled with a great number of cartilaginous bodies of variable size, almost all of which were free. There was no doubt that by the accumulation of these cartilaginous bodies the head of the femur had gradually been pushed out from the socket. Body for body was carefully removed until the ground of the acetabulum was visible. It showed exactly the same changes in the synovial tissue as were seen in the fovea capitis, with the exception that they were much more extensive. The acetabular cavity was thoroughly curetted until one could be sure that all the diseased portions were radically removed. It was tiresome to remove all the tiny joint bodies, because a great many were hidden in the different reflexions of the capsule. Three hundred and ninety-five free bodies were counted; the smallest ones were still attached to the synovial membrane, like corals to a reef. The head of the femur was then reduced, and the wound was closed in layers.

Unfortunately, a postoperative streptococcic infection developed, which necessitated wide and multiple drainage of the hip joint. The patient is now recovering from the infection, but it is doubtful how much useful motion he will preserve in the hip.

The histologic picture resembled in many respects that seen in case 1, but the process was not quite as advanced. Here too one could notice that the first stages in the formation of the cartilaginous bodies consisted in the appearance of a cartilaginous ground substance between the cells and the fibers of the synovial connective tissue. In this case, however, the ground substance had a clearly basophilic character from the beginning; it was pale blue even in those areas where the cells showed still more resemblance to fibrocytes than to cartilaginous cells and where, because of the incomplete impregnation of the collagenous fibers, the newly formed cartilage had to be classified as a more primitive fibrous cartilage.

Within this fibrous cartilage, certainly at the same time and in different places, there was marked proliferation of certain cells which more and more

assumed the appearance of mature cartilaginous cells and showed a definite tendency to group formation. The different cartilaginous centers, of more mature structure and showing very active proliferation, expanded in centrifugal direction. The cellular activity was evidently the main factor in promoting the growth, even the increment of the ground substance, for which, as one could see over and over again, mainly the necrosis and disintegration of the cell groups and their transformation to ground substance were primarily responsible. The necrosis of cartilaginous cells occurred apparently very rapidly, and the same was true with their assimilation to hyaline ground substance. The centrifugal direction of the growth of the cartilaginous foci or bodies could easily be recognized also from fields of degeneration in the oldest, i. e., central areas of greater cell growth, where the so characteristic form of asbestos degeneration of cartilage was a frequent finding.

It was also interesting to observe that the foci of hyaline cartilage, which resulted from localized increased proliferative power of certain cells of the primary fibrous cartilage, extended later within and toward the mother soil. The foci of hyaline cartilage were then found, with sharply outlined convex globules, bordering either on the primary fibrous cartilage or on the synovial fibrous tissue, thus compressing and gradually replacing the mother tissue.

All the free bodies were made up only of hyaline cartilage. Calcification was an extremely rare finding. Beginning deposition of lime salts was seen in only a few places. It was arranged in wreathlike fashion around the cell groups and from here gradually extended into the septums of hyaline ground substance. Bone formation did not occur in any of the bodies that were examined.

Case 3.—A man aged 52 complained of pain in the left hip. Clinical symptoms started more than two years before admission to the hospital, when he slipped on a greasy floor and fell. He hobbled about and had to go home in a car. He was in and out of bed during a period of about three weeks; then he tried to work for two days but was unable to do so. The hip and back were strapped. He was kept in a hospital, where traction was applied for six days; he then wore a plaster cast for four weeks. After that time he was worse than before. The hip and knee joints stiffened.

On physical examination the patient appeared to be in good health. The left hip joint was kept in a position of 25 degrees of flexion, 10 degrees of abduction and 30 degrees of external rotation. There was only 25 degrees of free flexion motion.

Roentgenograms taken at different times before the patient's admission to the hospital revealed the following conditions:

Four weeks after the onset of the symptoms (fig. 8*A*) a calcified joint body the size of a bean was present at the inferior aspect of the proximal end of the femur, being separated from the neck by a narrow zone of 1 mm. One pole of the body was sticking in a small troughlike impression at the joint margin of the head of the femur. The other pole of the body was apparently in connection with another smaller body of lesser density, which was partially hidden by the cortex of the neck. There were only mild hypertrophic arthritic changes of the left hip joint, those on the right being a little more marked, with exostoses at the inferior part of the acetabulum.

Ten months after the onset (fig. 8*B*) the two bodies at the inferior aspect of the head of the femur were still present, practically unchanged. A third body of the same structure had appeared, inferior to the margin of the joint. The joint space was well preserved.

Thirteen months after the onset the three bodies had apparently united and formed a sharply outlined, not densely calcified body in the inferior portion of the joint.

Two years after the onset (fig. 8 *C*) the calcified mass in the hip joint had increased remarkably in size and was forming a tumor which filled the entire lateral compartment of the joint, extending laterally to the greater trochanter.

At the time of admission the picture was the same as previously described.

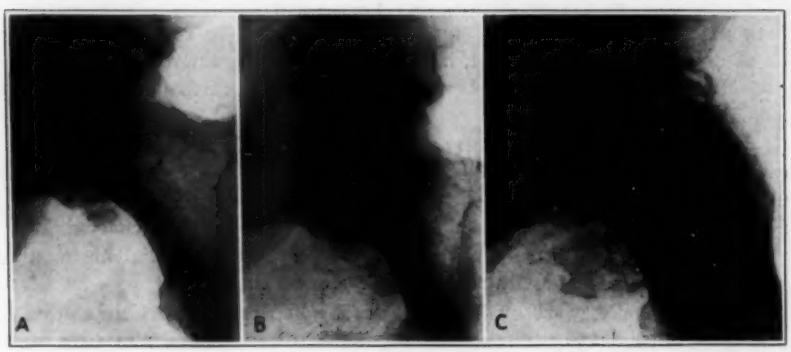

Fig. 8 (case 3).—Pictures taken at intervals showing the development of the big cartilaginous-bony intra-articular mass. There are mild hypertrophic arthritic changes of the hip joint.

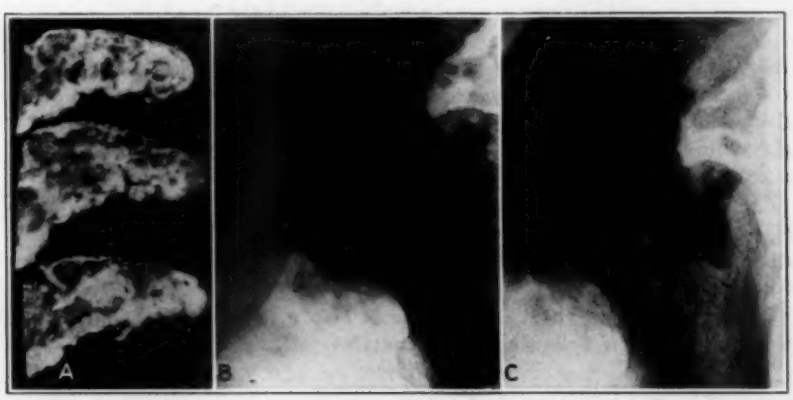

Fig. 9 (case 3).—Pictures taken after incomplete surgical removal of the intra-articular tumor. There was ossification above the hip joint after stripping of the periosteum. *A* shows three slices through the tumor. The lobulated surface is covered by mature hyaline cartilage and the central bony areas.

The whole series of roentgenograms strongly suggested chondromatosis of the hip joint as a diagnosis. Removal of the bodies was indicated.

The hip joint was opened by an anterolateral incision. There was a large mass of cartilaginous-bony consistency, lobulated (fig. 8) and covering the lateral portion of the neck anteriorly and inferiorly. It measured about 5 by 4 by 2 inches (12.7 by 10 by 5 cm.). It was entirely intracapsular and was not attached

firmly in any place, and could be removed relatively easily. The capsule was thick, but the synovial membrane did not show more marked pathologic changes. The joint cartilage of the head of the femur appeared to be normal. There was full range of motion as soon as the tumor was removed. After the operation, with the patient under general anesthesia, two manipulations were performed to increase the amount of motion. Half a year later he felt much improved and had a good range of motion. The leg was, however, kept in considerable external rotation.

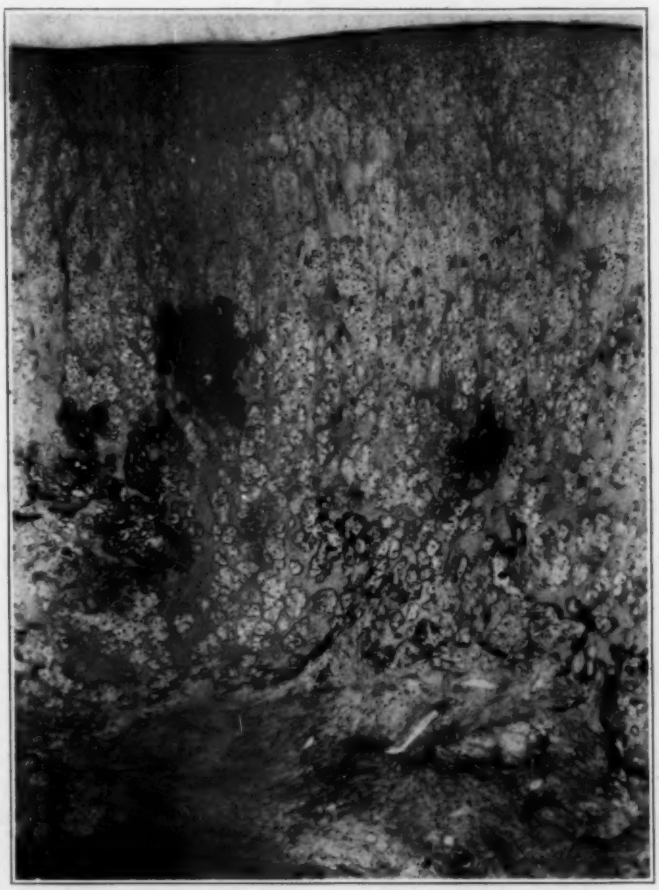

Fig. 10 (case 3).—Photomicrograph of the cartilaginous cover with proliferation of the deeper cellular layers, irregular calcification of ground substance in the deeper strata, especially around the cell groups, and vascular resorption of cartilage, not followed by ossification.

Roentgenograms taken half a year after operation (fig. 9*B*) revealed that a part of the calcified tumor had remained in the inferior compartment of the joint, where it had led to definite pressure atrophy of the neck of the femur. There was irregular ossification of the superior aspect of the neck, a result of the stripping of periosteum at the time of operation.

The patient was seen two years after the operation. He was complaining of weakness and pain of the left lower extremity, which was kept in 30 degrees of external rotation and 40 degrees of flexion contracture. There was flexion of 45 degrees, but all other movements were abolished. He walked with a marked limp.

Roentgenograms (fig. 9 *B*) showed that the portion of the tumor which had remained in the joint had apparently fused to the inferior surface of the neck. It was definitely smaller and had more regular structure. It was most likely that the cartilaginous mass had become ossified and that the whole process had come to a standstill.

The pathologic examination of many different portions of the tumor showed a picture which resembled closely that of osteochondroma. The densely lobulated

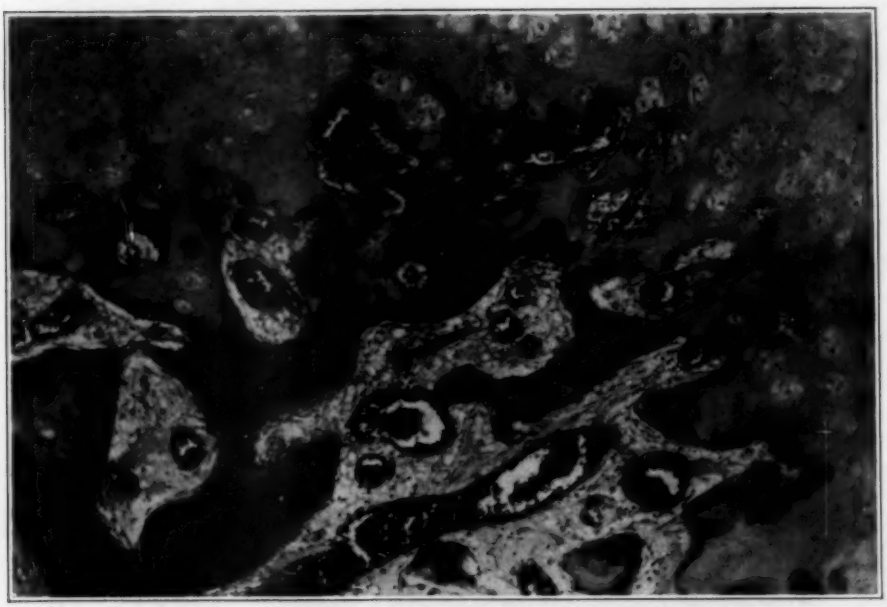

Fig. 11 (case 3).—Photomicrograph of enchondral ossification at the lower surface of the cartilaginous cover. There is no column formation of proliferative cartilage. An irregular zone of calcification and pronounced vascular resorption with osteoblastic bone apposition are seen.

mass had a relatively thick cover of hyaline cartilaginous tissue, which showed considerable proliferative activity of the deeper cellular layers, whereas the more superficial layers with their small and flattened cells gradually blended into fibrous tissue, which could be considered as perichondrium. The fibrous tissue between the lobules was relatively dense and very vascular—a certain sign that the tumor had been attached to its adjoining area, i. e., either to the joint capsule or to the neck of the femur. The cartilaginous cover of the tumor showed enchondral ossification from below, which in some places was quite active. The bony tissue was coarse and in rapid process of structural transformation. The narrow spaces contained hyperemic and edematous loose fibrous bone marrow.

COMMENT

I do not intend to discuss here in a general way the clinical and roentgenographic picture of chondromatosis of the joints. It has been done before, and a number of excellent articles are available (Rostock,[1] Henderson and Jones,[2] Eden [3] and Janker [4]).

From the clinical and the anatomic study of these three cases, I should like to make a few remarks concerning the pathogenesis of chondromatosis of the joints. (I prefer the term chondromatosis to osteochondromatosis, because, as case 2 showed definitely, the lesion may be advanced and still there may be no new bone formation.) Since Lexer's [5] article in 1907, the idea seems generally accepted that chondromatosis is derived from a blastomatous growth from many dispersed particles of cartilaginous tissue lying in the synovial membrane since its embryonal development. Although Lexer was able to explain a good many of the features of chondromatosis with his theory of embryonal germ dispersion, I do not think that he and his followers are correct. The histologic picture in the beginning stages of chondromatosis speak against considering chondromatosis as a blastoma. If Lexer were right, one would expect to find within the synovial connective tissue small centers of hyaline cartilage, by autonomous proliferation of which small chondromas develop. Later stages of chondromatosis may suggest such an origin. However, if one concentrates on the first histologic changes, one misses entirely the dispersed cartilaginous germs and finds a picture of impregnation of synovial connective tissue with cartilaginous ground substance. The cells included preserve for a while their character of fibrocytes, and the tissue resulting is therefore fibrous cartilage. As far as the cartilage growth is concerned, the process is rather diffuse from the start and not, as one would expect from Lexer's theory, circumscribed. Later, within the primary fibrous cartilage a more circumscribed proliferation of certain cells takes place. The cells gradually assume the typical picture of cartilage cells and assemble in groups, and larger areas of hyaline ground substance result chiefly from disintegration and homogenization of cartilaginous cells. Such centers of increased cellular activity gradually suppress and replace the fibrous cartilage from which they developed. At such a stage one could be induced to accept Lexer's idea.

Bone formation occurs secondarily in all the different ways, as ossification may be seen also in other places; enchondral ossification is fre-

1. Rostock, P.: Beitr. z. klin. Chir. **144**:58, 1928.
2. Henderson, M. S., and Jones, H. T.: J. Bone & Joint Surg. **5**:400, 1923.
3. Eden, R.: Arch. f. klin. Chir. **104**:277, 1914.
4. Janker, R.: Deutsche Ztschr. f. Chir. **211**:135, 1928.
5. Lexer, E.: Deutsche Ztschr. f, Chir. **88**:311, 1907.

quent, but more primitive forms suggesting metaplasia of cartilaginous into bony tissue are not rare.

The histologic picture of chondromatosis is essentially similar to that of myositis ossificans, in which cartilaginous and bony tissue develop in exactly the same way within the connective tissue of the skeletal musculature. Myositis ossificans has also been considered by some as a blastoma and by others as an inflammatory process (Reichel,[6] the first to describe chondromatosis, considered it also a contagious agent), which, infecting the synovia and spreading within the joint is thus leading to the picture of diffuse chondromatosis). There seems to be now more and more agreement (Macrycostas [7] and von Meyenburg [8]) concerning myositis ossificans, the theory being that it is neither a tumor nor an inflammatory process. Against the theory that it is a tumor are the facts that myositis ossificans, even if left unhindered, does not grow toward a spherical shape, its growth is not unlimited, it frequently comes to a spontaneous standstill and it may even completely disappear if the causative (mechanic-traumatic) factor is removed. One is therefore justified in considering myositis ossificans as a localized metaplastic hyperplasia of the connective tissue of the skeletal musculature. It is metaplastic, however, mainly in the sense that there is indirect metaplasia with simultaneous development of cartilaginous and osseous tissue in the common matrix of connective tissue.

I feel that the same is true with chondromatosis of the joints. Chondromatosis is not a blastoma of the joint capsule; the marked proliferative activity is not sufficient reason to classify the growth as a true tumor. It is just a hyperplastic process of synovial tissue in which the close embryonal relation to cartilaginous tissue becomes manifest. The external differences between chondromatosis and myositis are due mainly to the different localization of the processes. In myositis ossificans, the process is localized in the connective tissue of the musculature; in chondromatosis, in the synovial membrane, which undergoes the metaplastic changes, and, owing to the phylogenetic and ontogenetic relation of synovia to cartilage, there is greater tendency to cartilage formation in chondromatosis.

As myositis ossificans chondromatosis may appear as a localized and as a progressive or diffuse lesion, the entire joint capsule may show the hyperplastic changes or only a relatively small part of it (case 2). The process may remain limited to the synovial tissue (this is the rule), or it may expand, break through the fibrous joint capsule like a malig-

6. Reichel: Arch. f. klin. Chir., 1900, vol. 61.

7. Macrycostas: Arch. f. klin. Chir. **158**:584, 1930.

8. von Meyenburg, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, p. 391.

nant growth and involve also the connective tissue of the surrounding musculature (this is the rare exception illustrated by Lexer's case). These differences most likely depend only on the degree of differentiation the mesenchymatous tissue has taken in the neighborhood of the skeleton. If the genotypic potency of the simple fibrocyte to produce supporting substances of any type is not too latent, then any of the connective tissue of the body may produce cartilage or bony tissue by a hyperplastic metaplastic process, which is more extensive the closer it is situated to the skeleton.

In a number of instances of chondromatosis of the joints there is a gradual decline or even a complete disappearance of the joint bodies, as in cases of myositis ossificans. Cases 1 and 3 are good examples, and other cases have been reported in the literature. In cases 1 and 3, the operation did not succeed in removing completely the cartilaginous and bony masses; the roentgenograms taken after the operation showed a number of bodies remaining. Nevertheless, the roentgenographic follow-up study in both cases revealed a spontaneous diminution in the number and size of the remaining bodies. This shows clearly that the hyperplastic process exhausts itself gradually and the cartilaginous cells cease to proliferate, whereas ossification continues until all the cartilage has been removed—a picture similar to the physiologic process of enchondral ossification with the final disappearance of the epiphysial plates. The bony tissue may, later, also become completely resorbed by cellular (osteoclastic) activity. Such a fact speaks strongly against the possibility of the process being a tumor.

The histologic picture in case 1, with the numerous small lacunar particles of calcified material lying in the synovial fibrous tissue, gave a vivid impression of the rapid disappearance of calcified joint bodies by cellular activity. It could be also considered that some of the joint bodies became crushed during motion of the joint, and smaller fragments floated for some time in the synovial fluid. Later, they may have settled in small pockets or at the sites of reflexion of the synovial membrane and gradually become included and resorbed in the synovial layers. Similar pictures can be observed in any case of intra-articular fracture.

From this analogy between myositis ossificans and chondromatosis, one could conclude that in a number of cases of more clearcut traumatic origin the hyperplastic activity of the synovial connective tissue could be overcome by the seclusion of secondary traumatic irritating factors under immobilization and rest in the same way as it is so frequently with traumatic myositis in the region of the elbow. Further observation will be necessary to settle this question.

As far as the etiology of chondromatosis is concerned, it remains just as obscure as that of myositis ossificans. The cases reported here do not permit any new conclusion in this respect.

Unusual and worth the emphasis is case 2, in which the diagnosis could not be made before the exploratory operation. Despite the presence of 395 free joint bodies, calcification and ossification had not yet occurred in sufficient strength to cast a shadow in the roentgenogram. The head of the femur has been partially pushed out from the socket, and the joint was locked in abduction and flexion. This is the only case of advanced chondromatosis in which a typical roentgenographic picture was not obtained. None of the cases reported in the literature was of similar character.

The condition in case 3, which is somewhat unusual because of the relatively high age of the patient (50), started apparently multicentrically, probably in some hypertrophied tags of synovial tissue, and most likely on a traumatic basis. Later the different centers merged and formed one large mass of cartilaginous-bony tissue, which histologically showed the most mature differentiation, resembling closely the structure of a true osteochondroma.

SUMMARY

On the basis of material in three cases, which has been carefully studied clinically, roentgenographically and pathologically, the idea is expressed that chondromatosis of joints does not represent a blastomatous change of the synovial membrane. The process is similar to that of myositis ossificans—a metaplastic hyperplasia of connective tissue. The close embryonal relation of synovia to cartilage explains the prevalence of cartilaginous tissue in chondromatosis. Spontaneous resorption of calcified bodies speaks in favor of a hyperplastic process also from a clinical point of view.

USE OF HOMOLOGOUS BONE GRAFTS IN CASES OF OSTEOGENESIS IMPERFECTA

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Fractures in cases of osteogenesis imperfecta usually heal without difficulty, but at times, after repeated fractures at the same site, union is either by fibrous tissue or by a soft osteoid tissue. Patients with ununited fractures or with severe deformities of the bones of the lower extremities, some of whom are unable to walk, are seen not uncommonly. In such cases, both as a result of the basic pathologic condition and from atrophy of disuse, the bones are very small and weak, making weight bearing, even with braces, impracticable.

A situation of this sort, which occurred in an 11 year old girl with severely deformed, ununited femurs, who never had walked, was the reason for my experimenting with homologous bone grafts from the tibias of the patient's mother in an attempt to correct the deformities, bring about union in the femurs, and, at the same time, strengthen them sufficiently to permit the child to walk. It was hoped that the stimulus of weight bearing might lead to further increase in the diameter and strength of the femurs, which could well be compared with clay pipe stems in size and brittleness. The success of the grafts in this case encouraged the use of the procedure in three other patients. In all, eight bones were operated on in four patients. The first operation was done on June 23, 1926, and the last on Sept. 19, 1935. With the exception of the last operation, which was done so recently that the result cannot be determined, the average time that has elapsed since each procedure is more than five years. Three of the patients were girls, aged 9, 9 and 10 years at the time of operation, and one was a boy, aged 13. Three femurs, four tibias and one humerus were operated on.

Onlay grafts from the donors' tibias were used in each case. In four operations one large graft was used, and in the other four two or more smaller grafts were employed. The periosteum was elevated from the bone over the area to which the graft was applied, and the latter was secured by several sutures of kangaroo tendon or chromic catgut, passed around the bone beneath the periosteum and around the graft. The grafts were used without periosteum and consisted of the full thickness of the cortex together with a layer of cancellous medullary bone.

From the New York Orthopaedic Dispensary and Hospital.

When a pseudarthrosis existed, this area was excised. In cases of severe deformity two osteotomies were done in order to secure better correction and alinement, and the grafts were made to extend beyond both ends of the intermediate fragment.

The two femurs of the first patient were immobilized by means of the Taylor traction hip splint, designed for the treatment of tuberculosis of the hip. Although the result was satisfactory, in all of the subsequent cases the extremity was immobilized in a plaster cast. After seven operations the graft united to and became amalgamated with the bone to which it was attached, and firm union took place at the site of the fracture or the osteotomy. In some cases, however, union was slow and became strong only after several months. In all the cases the bones hypertrophied after the application of the graft, and in three the increase in size was very substantial. All four patients were able to walk after operation, although two were obliged to use crutches or braces. One femur and one tibia in the same patient fractured two and five years subsequent to the application of the grafts. The graft which was applied to a humerus had united lightly at the end of nine weeks, but the final result is still to be determined.

In three cases the bone was obtained from one of the parents and in the fourth from an unrelated donor. Two of the donors, both parents, had the same blood groupings as the patients. The remaining two, one parent and the unrelated donor, were of different blood groups. This did not appear to affect the result, and on theoretical grounds it should not, since it is believed that the bone graft acts simply as a scaffolding for new bone to grow on and that it also affords a supply of calcium. In two instances enough bone for two operations was removed from the donor. The excess was placed in a large sterile test tube and refrigerated until the second operation several weeks later. The bone was then placed in an autoclave before it was used. The results with these grafts were as satisfactory as with fresh ones.

The calcium, phosphorus and phosphatase contents of the blood were within normal limits in all four patients, as has been found in other patients with this condition. The mother of one patient had had osteogenesis imperfecta during childhood. There was no familial history in the other cases.

SUMMARY AND CONCLUSIONS

1. Four patients with ununited fractures and severe deformities of the bones of the lower extremities which completely prevented or seriously interfered with walking and with one deformed humerus with recurring fractures were treated with onlay bone grafts from the tibias of donors, after correction of the deformities.

2. In the seven operations on the lower extremities the grafts united, and the resulting correction of the deformities and hypertrophy of the bones enabled the patients to walk. The result of a similar operation on a humerus cannot yet be determined.

3. It is believed that a homologous bone graft can be used to advantage in such cases or in any case in which a bone graft is indicated and in which an autogenous graft cannot be obtained.

REPORT OF CASES

CASE 1.—M. V., a white girl aged 8 months was admitted to the New York Orthopaedic Dispensary and Hospital on Feb. 27, 1917. She was said to have been born with a fracture of each leg. Subsequently she fractured her right arm, which

Fig. 1.—Ununited fracture of both femurs in a patient 11 years of age. The patient never had walked.

united. On her admission there was a fracture of the right femur. This was treated with a plaster spica, and union occurred. In September 1917 she sustained a fracture in the upper third of the right femur. She was admitted to the ward for reduction of a fracture of the left femur in December 1917. A marked anterior and lateral bowing at the junction of the middle and the upper third of the left femur was corrected by manipulation in August 1918. Braces were subsequently applied. A fracture occurred at the junction of the upper and the middle third of the right femur in November 1924.

The patient was readmitted to the hospital on April 14, 1926, at the age of 9. She was short, with a large cranium and blue scleras. There was marked angular deformity at the site of ununited fractures at the junction of the upper and the middle third of the shaft of each femur. The child had never walked. By means of a Taylor traction hip splint the angle of deformity of the left femur was reduced

from 90 to 30 degrees, and a corresponding correction was obtained on the right side. On June 23 an open reduction of the fracture of the right femur and application of bone graft were done. The shaft of the femur was not more than 1.5 cm. in diameter, and the bone was extremely brittle. Three centimeters of bone was resected, including the site of the fracture and the fibrous tissue joining the ends of the fragments. In exposing the upper fragment, it was fractured about 4 cm. from its end, leaving a loose intermediate piece of bone. A large full thickness graft, about 3 by 12 cm., from the tibia of the patient's mother was then secured to the upper, lower and intermediate fragments with four sutures of kangaroo tendon. A Taylor traction hip splint was applied. Union of the graft to the femur took place gradually, being fairly firm in about five months.

Fig. 2.—Application of a graft from the mother's tibia to the right femur after resection of an area of pseudarthrosis; anteroposterior view.

On Feb. 15, 1928, the site of fracture of the left femur was exposed, and a wedge of bone, including the fibrous pseudarthrosis, was removed. A large tibial graft, 3 by 10 cm., from the mother's tibia was secured to the upper and lower fragments with four kangaroo tendon sutures. A Taylor traction hip splint was applied to the extremity. Union between the graft and the femur was very slow but was sufficiently strong in October 1928 for the patient to walk for the first time, with the aid of braces. She was discharged from the hospital on November 15. She was last examined on Feb. 16, 1933, at which time the femurs were comparatively well developed and strong. She was walking without braces.

Case 2.—E. F., a 2 year old girl, was brought to the outpatient department of the New York Orthopaedic Hospital on April 3, 1922, with active rickets and a

deformity of the left tibia due to an old fracture. The patient's mother and a sister had several fractures during childhood, and both have blue scleras. She continued to have numerous fractures of the lower extremities, resulting in increasing deformities. She was admitted to the hospital in March 1930, at the age of 10 years, for the correction of marked anterior bowing of the left tibia. There was an ununited fracture at the junction of the middle and the lower third. On April 14 osteoclasis was done, producing a fracture above the site of nonunion and further correction at the pseudarthrosis. On May 5 the tibia was exposed, and the fibrous tissue and eburnated bone were resected from the site of the fracture, and better alinement was secured. Two pieces of bone 6 inches (15 cm.) long, ½ inch (1.3 cm.) wide and ¼ inch (0.6 cm.) thick, which were taken from the father's tibia, were tied on each side of the upper, lower and intermediate fragments with kangaroo tendon. The periosteum was sutured over the tibia, and grafts and a plaster cast were applied. The father's blood was not compatible with the patient's. Roentgenograms made seven weeks after operation showed union between

Fig. 3.—Graft from the mother's tibia applied to the left femur after resection of an area of pseudarthrosis. The condition of the right femur is shown eighteen months after application of the graft.

the bone grafts and the distal fragment of the tibia but not with the proximal fragment. On July 21 the child fell from a chair and fractured her left femur. Traction was applied, but the position of the fragments was unsatisfactory. On August 8, three months after operation, the grafts were completely united to the left tibia. On August 18 an open reduction of the left femur was done, and three pieces of bone, which had been removed from the father's tibia on May 15 and subsequently refrigerated in a sterile tube, were tied with chromic catgut to the femur. A plaster spica was applied to the left lower extremity. On November 8, six months after the operation on the tibia and two and one-half months after application of grafts to the femur, the spica was removed, and a posterior splint was applied. Union was present in the femur and the tibia, although slight bending of the tibia was possible. Roentgenograms showed union of the grafts to both the femur and the tibia. Following this, a transverse fracture occurred in

the left tibia below the grafts. This united. The child was discharged from the hospital on June 22, 1931, thirteen months after the operation on the tibia. Weight bearing was not yet permitted but was begun in October 1931. Braces were advised, but the parents refused to have them. On June 19, 1932, she fell, fracturing the middle third of the shaft of the left femur and the middle third of the right tibia and fibula. There was no displacement of the latter. The femur was treated by traction. During the next two years the left femur and tibia, to which the grafts had been applied, became larger and stronger. A marked

Fig. 4.—The result nine years after operation on the right femur and seven and one-half years after that on the left femur.

anterior bowing of the right tibia and fibula developed and on Oct. 6, 1933, this was corrected by osteotomy without the use of bone grafts. A section of bone 1½ inches (3.8 cm.) long was removed because the left lower extremity was 2¾ inches (7 cm.) short. Union occurred but was slow in taking place. The patient began to walk again five months after the operation. Braces were then applied. In spite of the fact that the bones of the legs continued to develop and become larger, she sustained a fracture of the tibia and fibula on each side as the result of a fall on April 23, 1935. The fractures united without difficulty.

CASE 3.—A. V., a 5 month old boy, was admitted to the outpatient department of the New York Orthopaedic Hospital with a fracture of the right femur. Following this he was not seen until 1926, when he returned with marked deformities of the lower extremities from numerous fractures. He never had been able to walk. There was marked angulation anteriorly and laterally in the upper third of each femur and anterior bowing of the left tibia. He presented the typical appearance of osteogenesis imperfecta, with a large cranium, blue scleras and a barrel chest. In July 1927 osteotomy of the left tibia was done for increasing deformity. In November 1927 braces were made, and with these and additional support the patient was able to stand and take a few steps. He continued to have numerous fractures of his lower extremities and of the bones of the right forearm. The anterior bowing of the left tibia recurred and progressed. The patient was admitted to the New York Orthopaedic Hospital in October 1931, at the age of 13, for correction of the deformity of the left tibia and application of a heterogeneous bone graft from a donor procured by the parents. The donor was not related to the patient, and his blood was not compatible with the patient's. On October 5 a section of bone ½ inch (1.3 cm.) thick was removed from the left tibia at the junction of the lower and the middle third, including the site of previous fracture. The marked bowing in the upper two-thirds was corrected by another osteotomy with removal of a wedge. The ends of the fragments were notched together. A graft 6 inches (15 cm.) long by 1 inch (2.5 cm.) wide from the tibia of the donor, was sutured with chromic catgut to the medial surface of the upper and lower fragments of the tibia, bridging the intermediate fragment. Several smaller grafts were placed on the outer side of the tibia and secured by chromic catgut placed around the tibia and the grafts. The periosteum could not be closed, but the bone was covered with subcutaneous fat and skin. A plaster spica was applied. The sutures were removed at the end of twelve days, at which time the wound had healed by primary union. A long leg plaster cast was substituted for the spica at the end of twelve weeks. At this time union appeared firm both by physical and by roentgenographic examination. Only a trace of callus was apparent between the tibia and the graft, however. The plaster cast was removed five weeks after operation. The alinement of the left lower extremity was now fair, with slight valgus of the lower end of the tibia. Union of the tibia was present, but the grafts appeared smaller, as though undergoing absorption. Six and one-half months after operation the patient was allowed up in braces. Eleven months after operation the smaller grafts had become incorporated with the tibia and the larger one was united at each end. The patient was last seen in September 1935, at which time union was firm in the left tibia and there was a moderate degree of anterior bowing. He was able to walk short distances by using two crutches; he was greatly impeded by his immense obesity. He had just sustained a fracture of the right humerus but had had no further fractures of his tibias.

CASE 4.—R. D., a 3 year old girl, was first seen in the clinic of the New York Orthopaedic Dispensary and Hospital on Sept. 1, 1927. The left femur had been fractured at birth, and subsequently she had had four fractures of each femur. She was the typical picture of osteogenesis imperfecta, with a large cranium, blue scleras, a barrel chest and marked deformity of the femurs. She had not walked. In July 1928 leg braces were applied, with which she afterward learned to walk. The left tibia was fractured in May 1933. She was admitted to the hospital on September 5 for correction of marked anterior bowing of the tibias. On September 8 a wedge was removed from the lower fourth of the left tibia, and two onlay grafts 3/16 inch (0.5 cm.) wide, which were removed from the mother's tibia, were

tied to the patient's tibia. A plaster cast was applied. On September 25 the right tibia was operated on. Because of the marked anterior bowing, two wedge-shaped osteotomies were performed, one at the lower fifth and the other at the junction of the upper and the middle third of the tibia. An onlay graft 6 inches (15 cm.) long and ¼ inch (0.6 cm.) wide was applied. This had been removed from the mother's tibia at the time of the first operation, seventeen days before. It was preserved in a sterile test tube in a refrigerator and was autoclaved before being used. Plaster casts were removed on February 14. Union had occurred in each tibia, and the grafts had united, but the bones were very small and fragile. One week later a fracture occurred in the lower end of the left tibia at the lower end of the graft. This united without delay. Roentgenograms made in June 1934 showed increased calcification of the tibias and decreased calcification of the femur. The patient was allowed to stand in long leg braces in July 1934, but in August a plaster cast was again applied because of a fracture of the right femur, which took place in bed. Five fractures of the left humerus occurred between August 1934 and July 1935. Although the deformities of the tibias partially recurred, these bones were not fractured after the bone grafts were applied. On Sept. 19, 1935, because of six recurrent fractures in the middle of the shaft of the left humerus, an onlay graft from the mother's left tibia was applied to the humerus without attempting to correct the slight angulation present. The calcium, phosphorus and phosphatase values of the blood were normal in this patient. The mother's blood was compatible with that of the patient.

TRAUMATIC RUPTURE OF A CONGENITAL CYST OF THE CHOLEDOCHUS

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In the presentation of a case of traumatic rupture of a congenital cyst of the choledochus, we believe that we are reporting a case unique in medical history. We have found, after a rather careful search of the literature, reports of only 130 accepted true cases of congenital cyst of the choledochus, and in none of these was there a history of traumatic rupture. Wright,[1] in reporting a case of cyst of the choledochus diagnosed by roentgenographic examination, made only casual mention of another of his cases in which the patient died from rupture of a congenitally dilated common duct after a fall from a bicycle, but this case has not been recorded elsewhere in the literature. Over a period of twenty years, Judd and Greene,[2] of the Mayo Clinic, found only one cyst of the choledochus in a series of 17,381 consecutive operations on the bile duct. Lavenson [3] stated that the first congenital cyst of the common bile duct was found by Vater in 1723.

The etiology of the condition is obscure, but it is generally considered to be of embryopathologic origin. These cystic dilatations vary in size from one 3 cm. in diameter to a cyst large enough almost to fill the abdominal cavity. The duodenal intramural portion of the duct is, as a rule, of normal size; likewise, the gallbladder and the hepatic ducts are usually normal.

The congenital aneurysmal dilatation of the common duct differs markedly from the ordinary type of dilatation found as a result of stones, stricture of the common duct or tumor of the head of the pancreas. In the usual types produced by internal or external pressure,

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1. Wright, A. Dickson: X-Ray Appearances Produced by Congenital Cystic Dilatation of the Common Bile Duct, Brit. J. Radiol. **8**:227-230, 1935.

2. Judd, E. Starr, and Greene, E. I.: Choledochus Cyst, Surg., Gynec. & Obst. **46**:317-324, 1928.

3. Lavenson, R. S.: Cysts of the Common Bile Duct, Am. J. M. Sc. **37**:563-570, 1909.

the biliary passages and the gallbladder enlarge as a whole, in accordance with Courvoisier's law; in the congenital type, on the other hand, the enlargement simulates local aneurysmal saccular dilatation.

Zinninger and Cash [4] in 1932 made an excellent review of the literature and found 82 cases which they accepted as true cases. They added a report of their own case. Gross [5] in 1933 reviewed 50 cases of idiopathic cyst of the choledochus in childhood and added reports of 2 cases of his own. He also reviewed 14 other cases not mentioned by Zinninger and Cash. In a review of the foreign literature [6] we have been able to find reports of 33 cases since 1933 that have not been mentioned by the American authors. In 1934 Weber [7] reported a case which was particularly interesting to us because of the presence of a slitlike tear in the wall of the cyst; however, no history of injury was obtained, and the patient died in a state of cardiac decompensation. At autopsy, the rupture was found to be due to colliquative degeneration of the hyaline fibrous tissue in the wall of the cyst. Swarthey and Weeder [8] in 1935 added the report of another case, that of a cyst of the choledochus with double common bile duct.

In the reported cases, palpable tumors of varying sizes, intermittent attacks of jaundice and pain have been prominent and common findings. Of the 130 cases on which the literature was available, the condition occurred most frequently in females in the ratio of 99 females to 27 males. (In 4 cases the sex was not given.) In 44 of the cases the age ranged from birth to 10 years; in 31, from 11 to 20 years; in 32, from 21 to 30 years, and in 11, from 31 to 40 years; in 10 cases the age was over 40. (The age was not given in 2 cases.) Of the 119 reported cases in which surgical treatment was employed there

4. Zinninger, M. M., and Cash, J. R.: Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. **24**:77-105 (Jan.) 1932.

5. Gross, Robert E.: Idiopathic Dilatation of the Common Bile Duct in Children, J. Pediat. **3**:730-755, 1932.

6. (*a*) Backer-Grøndahl, N.: Om idiopatisk choledochuscyste, Med. rev., Bergen **50**:337-354, 1933. (*b*) Djørup, Frans: On Idiopathic Dilatation of the Choledochus, Acta chir. Scandinav. **74**:479-480, 1934. (*c*) Murata, M.: Ueber einen dauernd geheilten Fall von idopathischer Choledochuserweiterung, Zentralbl. f. Chir. **62**:1269, 1935. (*d*) Sénèque, M. J.: Dilatation congénitale du canal cholédoque, par M. A. Tailhefer, Bull. et mém. Soc. nat. de chir. **60**:8-11, 1934. (*e*) Tavernier, M.: Dilatation congénitale du cholédoque, Lyon chir. **31**:595-597, 1934. (*f*) Ugelli, L.: Sulle dilatazioni congenite del coledoca, Policlinico (sez. chir.) **40**:343-355, 1933.

7. Weber, F. Parkes: Cystic Dilatation of the Common Bile-Duct, Brit. J. Child. Dis. **31**:27-36, 1934; Further Remarks on Cystic Dilatation of Common Bile-Duct, ibid. **31**:113-115, 1934.

8. Swarthey, William B., and Weeder, S. Dana: Choledochus Cyst with a Double Common Bile Duct, Ann. Surg. **101**:912-920, 1935.

was a mortality of 56 per cent. The condition in the remaining 10 cases was found at necropsy. In 1 case, diagnosed roentgenographically, treatment was not given.

REPORT OF A CASE

History.—R. P., aged 14 years, was admitted to the accident ward of the John Sealy Hospital at 10 a. m. on Dec. 3, 1935, complaining of severe pain in the upper part of the abdomen. About fifteen minutes prior to admission he had fallen out of a swing in the public park, striking the upper part of his abdomen across the back of a park bench. There were immediate abdominal pain and vomiting. His past medical history and the family history were unimportant.

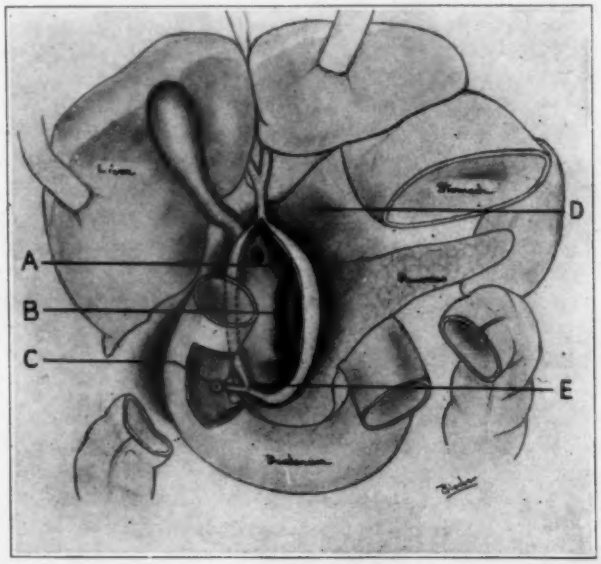

Fig. 1.—Schematic drawing of a traumatic rupture of a cyst of the congenital choledochus. The congenital cyst is indicated by *A*, the laceration in the wall of the cyst by *B*, the ampulla of Vater by *C*, extravasated bile and blood in the retroperitoneal cellular spaces by *D* and the junction of the canal of Wirsung with the common bile duct by *E*.

Examination.—Physical examination revealed a pale Mexican boy, with anxious facies. He was very restless and tossed about on the examining table. Profuse sweating and cold, clammy skin were prominent features. A few minutes later he became quiet and lay rather listless with half closed eyes. The temperature was 97.6 F., the blood pressure 130 systolic and 90 diastolic, the pulse rate 96 and the respiratory rate 30. There was considerable pain on pressure over the whole abdomen, but it was more pronounced in the epigastrium. Muscular rigidity was marked. Dulness over the liver was still present. Rectal examination gave negative results. A specimen of urine was clear.

A tentative diagnosis of ruptured viscus was made, and the patient was taken to the operating room for immediate laparotomy.

Operation.—A right rectus incision, about 2½ inches (6.3 cm.) in length, with its center at the level of the umbilicus, was made. The right rectus muscle was split in the line of its fibers. When the peritoneal cavity was opened, dark, straw-colored, odorless fluid was encountered. Since this fluid was recognized as a bile-stained transudate, the incision was extended upward to expose the biliary system. The gallbladder was found to be normal, and exploration of the liver revealed nothing unusual. The gallbladder and the liver were retracted upward, exposing the duodenum and a paraduodenal retroperitoneal hemorrhagic area. This area extended around the first and second portions of the duodenum, upward to the peritoneal reflection from the liver and laterally to the hepatic flexure of the colon. Incision through this layer of peritoneum showed the retroperitoneal cellular spaces to be engorged with this same type of bile-stained fluid.

At this point the patient's condition seemed to change for the worse. His pulse became more rapid, and the respirations were labored. We felt that there possibly had been a retroperitoneal rupture of the liver or bile duct, but also that the patient's condition did not warrant further exploration at this time. A stab wound was made in the right flank under the edge of the liver, and a soft rubber tube with two cigaret drains were placed in the area of retroperitoneal extravasation. The abdomen was then closed.

Immediately after the operation the patient was given 1,000 cc. of physiologic solution of sodium chloride by hypodermoclysis and 50 cc. of a 50 per cent solution of dextrose intravenously. Continuous decompression of the upper intestinal tract with a modification of the Wangensteen apparatus was also started. In spite of the foregoing measures and other routine treatment for shock, the patient died at 5:30 a. m. the next day. Permission for necropsy was obtained.

Macroscopic Examination.—Postmortem examination revealed no external lesions except the operative incisions in the wall of the abdomen. The boy was normally developed and in an excellent state of nutrition. Nearly 300 cc. of thin reddish brown fluid was found in the peritoneal cavity. The left lobe of the liver extended up, forming a peculiar hornlike projection. On the anterior and superior surfaces of the liver, a thin layer of yellow material grossly resembling bile was found. This material was also found on the inferior surface of the liver and on portions of the duodenum and pancreas.

The gallbladder was in its normal position, the tip of the fundus reaching the anterior margin of the liver. It was not enlarged. In the retroperitoneal tissues in the region of the superior border of the duodenum there was a large, greenish, fluctuant mass from which yellow fluid resembling bile could be expressed. This mass appeared to be a quantity of extravasated fluid (bile) which had dissected up the peritoneum and was seeping through into the peritoneal cavity. When the gallbladder was opened the wall was found not to be thickened, measuring from 2 to 3 mm. in thickness, and the mucosa presented no gross abnormalities.

The cystic duct could be probed with large scissors, indicating unusual dilatation. The circumference of the cystic duct was nearly 2 cm., and the thickness of the wall at this point was slightly less than that of the gallbladder. There were folds or false pockets in the mucosa of the cystic duct, which were interpreted as remnants of the spiral valve of Heister.

The hepatic ducts and the common hepatic duct did not appear to be dilated. The common bile duct was found to be a cystic mass containing dark, greenish bile. On the inferior surface, somewhat to the left side, a rupture measuring about 4 cm. in length was found. The base of the rupture was dark and ragged.

The tissue at the base of the rupture was closely associated with the greenish mass described about the superior border of the duodenum. The bile had apparently dissected up between the duct and the first portion of the duodenum. Bile also dissected through the soft tissue to the surface of the pancreas and along the peritoneal surface of the lesser peritoneal sac, but search revealed no rupture into the lesser pouch. The common duct measured 7 cm. in length, and the circumference averaged from 5 to 7 cm. The greatest circumference could be found as the ampulla was approached. The wall of the common duct was from 1 to 2 mm. in thickness. The mucosa seemed definitely thinner than that found in the gallbladder.

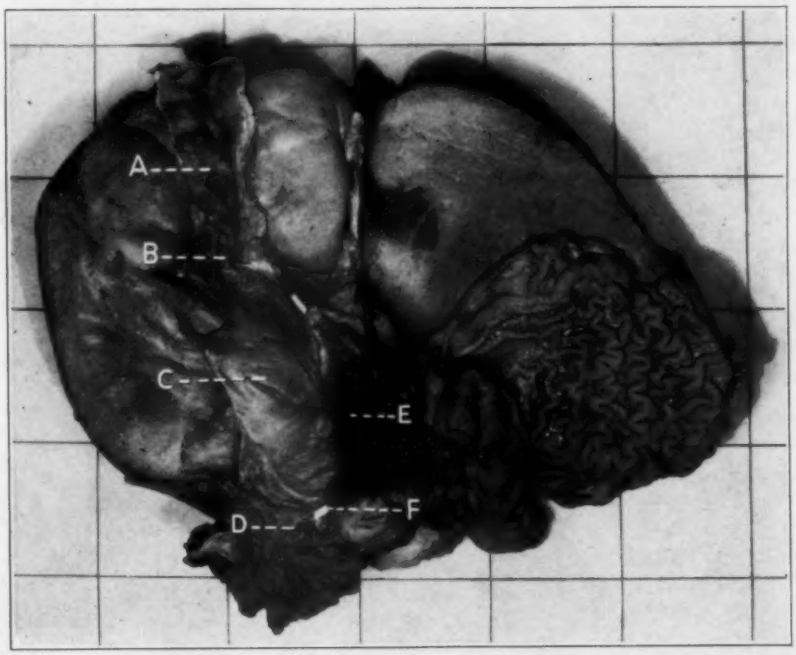

Fig. 2.—Photograph of a fixed specimen. *A* indicates the gallbladder; *B*, the cystic duct; *C*, a congenital cyst of the choledochus; *D*, the ampulla of Vater; *E*, the point of rupture of the cyst, and *F*, the junction of the pancreatic and the common bile duct.

The common duct joined the pancreatic duct through a narrow orifice at a point 2 cm. from the common orifice in the duodenum. Rather striking was the fact that the ampulla of Vater, or the common passage of the pancreatic and common bile duct, was at right angles to the common bile duct and seemingly a continuation of the duct of Wirsung. In this case, one might easily consider that the common bile duct opened into the pancreatic duct. The duct of Santorini was normal.

The liver was normal. Further examination revealed no rupture of the viscera. The heart and lungs were normal. No other anomalies were found in the body.

Microscopic Examination.—There was a little fat necrosis in the omental tissue and rather marked peritoneal inflammation in the areas nearest the rupture. In the lungs there was found some bronchopneumonia and congestion.

There was considerable bile around the pancreas, to which attention was called in the gross description. Areas of acute inflammation were found in the pancreatic tissue.

Fig. 3.—Photomicrograph of the wall of the cyst, showing the absence of muscle fibers and the increase of fibrous tissue.

The liver was normal in all respects. The gallbladder showed the usual post-mortem changes in the epithelium and mucosa but was otherwise normal. The

common duct was lined with cuboidal epithelium, which was definitely flattened as compared with normal. There was a rather mild chronic inflammatory reaction throughout the duct, and the lymphatic vessels were engorged with lymphocytes. The wall of the duct was composed of the lining epithelium (which in some areas was deficient), a relatively thick wall of fibrous tissue and the serosa. No muscle fibers could be identified in the walls of the duct.

COMMENT

The literature gives little information concerning the relation of the pancreatic duct or ducts to a cyst of the choledochus. Sénèque and Tailhefer [6d] list cases in which the enlargement of the cyst of the choledochus occurred so near the ampulla that the pancreatic duct opened directly into the cyst.

In the case which we have presented, the pancreatic duct and the common bile duct had a common lumen for a distance of 3 cm. before entering the duodenum. That the cyst exerted no influence on the ampulla seemed certain. There were no obstructions, strictures, tumors or inflammatory processes in the biliary passage. We feel that this case goes far toward substantiating the assumption that these cysts are congenital. A large dilated cyst had developed, and yet the patient failed to suffer any discomfort at this early period. Undoubtedly, if the cyst had continued to enlarge, the patient would have experienced the pain and the gastro-intestinal symptoms described in the reported cases.

SUMMARY

We have presented, we believe, the only case of a cyst of the choledochus with traumatic rupture. The fact that our patient had no previous history of illness with reference to the biliary system substantiates the patency of his choledochus. We believe that this fact also marks the etiology as congenital, particularly in this case. The rarity of finding a cyst of the choledochus is exceeded only by finding one that has ruptured.

PREVENTION OF THE FORMATION OF URINARY CALCULI IN PATIENTS WITH ORTHOPEDIC PROBLEMS

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Reports in the literature of the association of urinary calculi and diseases of the bone have been confined chiefly to the presentation of cases, and in some instances analyses of the chemical composition of the calculi have been given. Occasionally the presence of infection in the urinary tract has been noted when calculi developed during a long period of immobilization. The formation of urinary calculi under such circumstances is not a rare and unusual complication, and a few cases have been reported and discussed from the etiologic standpoint, but little thought has been given to the nature of the disease and its prevention.

The physiochemical reactions which aid or prevent the formation of urinary calculi have ceased to be matters for conjecture, and it is now recognized that a deficiency in vitamin A, infection in the urinary tract, urinary stasis, hyperparathyroidism, phosphaturia, oxaluria and excessive quantities of uric acid definitely predispose to their formation. In view of the fact that many of these predisposing factors frequently occur in patients whose convalescence requires a long period of immobilization, the formation of calculi can be minimized by the use of dietary measures in addition to the other therapeutic measures usually employed.

The following case is one in which urinary calculi developed during a long convalescence, so that when the presence of stones was first recognized the kidney was destroyed to the extent that nephrectomy was required.

REPORT OF A CASE

History.—A man 24 years of age entered the Cleveland Clinic on Jan. 2, 1929, complaining of paralysis of the legs and a stone in the right kidney. In July 1927, eighteen months before admission to the clinic, the first lumbar vertebra was fractured in an automobile accident, and the patient immediately became paralyzed from below the level of the umbilicus. This was accompanied by loss of control of the bladder and rectum. In August 1927 bilateral thrombophlebitis of the legs developed, and soon after this laminectomy was performed. In November 1927 a roentgenogram had been taken because of acute cystitis, and a large calculus was seen in the right kidney. This had not been present in July, at the time of the injury, four months previously.

From the Cleveland Clinic.

In January 1928 the patient began to use crutches. There had been considerable improvement in the function of the lower extremities, but he had to wear braces because of paralysis of the muscles of the lower part of the legs. He had no control of the rectal sphincter but was able to start the flow of urine by pressing firmly over the bladder and tightening the abdominal muscles. Roentgenograms showed that the calculus was progressively increasing in size.

Aside from the usual diseases of childhood and pneumonia at the age of 16, the patient had always had excellent health.

Physical Examination.—When the patient was seen at the clinic eighteen months after his injury, physical examination showed him to be well developed and nourished and unable to walk without the use of braces and a cane. The scar over the lower dorsal and upper lumbar vertebrae was well healed. Considerable paralysis was noted below the site of the lesion, and a complete toe drop was present. There was a marked loss of tone of the rectal sphincter.

Urologic Examination.—A stereoscopic roentgenogram showed a large stone in the right kidney, which was moderately enlarged.

Cystoscopic Examination.—The cystoscope was introduced into the bladder with ease through a relaxed internal sphincter. The bladder, which had a capacity of 300 cc., contained 2 ounces (60 cc.) of cloudy residual urine. No stones, ulcer, tumor or diverticulum was present. There was a generalized diffuse chronic inflammation of the wall of the bladder. The bladder showed trabeculation, which may previously have been rather fine, but at the time of this examination was fairly thick. The examiner received the impression that this was a neurogenic bladder, the condition of which had been improving. Five cubic centimeters of indigo carmine was injected intravenously and was seen to appear from the right ureteral orifice in seven and one-half minutes with two plus strength and from the left orifice in four minutes with four plus strength. Catheters were passed to the pelvis of each kidney, and specimens of urine were secured for study.

After the injection of 18 cc. of sodium iodide, a pyelogram showed extensive hydronephrosis of the right kidney and a large stone in the pelvis, which filled the lower calices.

Laboratory Findings.—Examination of the blood showed 4,980,000 red cells, 5,950 white cells and 90 per cent hemoglobin. The sugar content was 82 mg., the urea content 24 mg. and the creatinine content 1.5 mg. per hundred cubic centimeters of blood. The Wassermann test gave a negative reaction.

Examination of the urine showed it to be alkaline in reaction, with a specific gravity of 1.016. It contained a trace of albumin but no sugar. There were numerous white blood cells but few red cells. No casts were present, but there were numerous phosphatic crystals.

The urine from the right kidney, which contained the stone, was alkaline in reaction. It contained many red blood cells and numerous phosphatic crystals but no white cells. Examination of the sediment was negative for organisms, and repeated cultures of the specimen gave negative results. The urine from the left kidney was slightly alkaline in reaction; it contained numerous red cells and a few phosphatic crystals but no white cells. The urine from the bladder was alkaline in reaction and contained many red cells and clumps of white cells. A culture of the specimen showed Bacillus coli and Staphylococcus albus.

Since the stone was not causing the patient a great deal of discomfort, permission for operative intervention was refused, but the symptoms increased, and on

Dec. 12, 1931, four years and eight months after the injury, nephrectomy was performed on the right side. Chemical analysis of the stone after its removal showed it to be composed chiefly of calcium phosphate.

At this time, we had completed our first experimental work on the use of a high vitamin A diet in the prevention of urinary calculi. Therefore, after operation, a modified high vitamin A acid ash diet was prescribed, and there has been no evidence of the further formation of calculi. The reaction of the urine has remained acid.

When the patient was admitted to the hospital after his injury, the urine was acid in reaction and no infection was present. One week later the reaction was alkaline, and it remained so throughout the entire period of immobilization. When the patient was first seen at the clinic, the urine was alkaline in reaction and was loaded with phosphates and phosphatic crystals.

Pyelogram showing extensive hydronephrosis of the right kidney and a large stone in the pelvis.

HISTORICAL SURVEY

In 1855 Virchow [1] first noted the relationship between destructive lesions of the bones and pathologic calcification. Although urinary calculi were not present in any of the cases cited, he believed that the metastatic deposit of calcium consisted of the same salts which, through resorption, had disappeared from the osseous lesions and that an excess of calcium salts in the blood or hypercalcemia was an important factor in the causation of such deposits.

1. Virchow, R.: Kalmetastasen, Virchows Arch. f. path. Anat. **8**:103, 1855.

The earliest reference to the association of the formation of renal calculi and conditions of the bone was noted by Bastion [2] in 1861. He reported the formation of calculi after a vertebral injury. In 1895 Müller [3] reported eight cases in which bilateral renal calculi developed after severe spinal injury. Cabot [4] in 1910 reported the formation of renal calculi after severe injury to the hip. In this instance a phosphatic stone was passed spontaneously, and later a stone was removed from the left ureter.

Paul,[5] working in the Department of Soldiers' Civil Reestablishment in Toronto, Canada, observed the frequent etiologic relationship between suppuration of the bone and the formation of urinary calculi. He presented twenty cases in which suppuration of the bone had occurred and found that the urine of approximately 90 per cent of the patients was infected. The average time which elapsed between the injury and the appearance of the first renal symptom was seventeen and seven-tenths months; the longest time was forty-five months, and the shortest, four months.

Mayet [6] in 1920 reported two instances in which renal calculi developed in a patient who was immobilized for a period of several years for Pott's disease and tuberculosis of the hip, respectively. In one of these cases the calculi were bilateral.

Taterka [7] in 1926 reported that bilateral renal calculi developed in a patient who had a gunshot wound in the cervical portion of the spine and in another with a vertebral injury due to a fall. Vesical calculi developed in one of these patients within six months after the injury.

In 1928 O'Conor [8] reported the formation of bilateral renal calculi and vesical calculi within five months after a crushing injury to the spine.

Reports of the association of urinary calculi and diseases of the bone have been presented more frequently since 1930. Although the "age of speed" may be conducive to a larger number of severe injuries, the apparent increase in incidence is probably due to the fact that physicians are more alert to recognize this complication.

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2. Bastion, cited by Abeshouse, B. S., in discussion on Holmes and Coplan,[24] p. 232.

3. Müller, K.: Ueber Nephrolithiasis nach Rückenmarksverletzungen, Verhandl. d. deutsch. Gesellsch. f. Chir. **2**:253-266, 1895.

4. Cabot, H.: Remarks on the Technic of Operations for Stone in the Ureter, Boston M. & S. J. **168**:789-791, 1910.

5. Paul, H. Ernest: Bone Suppuration, the Basic Cause of Renal Calculus Following War-Wounds, J. Urol. **9**:345-365 (April) 1923.

6. Mayet, H. H., cited by Brown and Earlam.[12]

7. Taterka, Hans: Ueber Steinbildung in den Nieren nach Wirbelsäulenverletzungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:661-666, 1926.

8. O'Conor, V. J.: Urological Complications Following Fracture of Spine: Case Report, J. Urol. **19**:721-728 (June) 1928.

In 1930 Borman [9] cited the case of a boy 9 years of age in whom renal and ureteral calculi developed after suppuration of the bone, and in the same year Schwarz [10] reported bilateral calculi accompanying suppurative lesions of the bone. Weber [11] in 1931 found renal calculi associated with suppuration of the bone in nine instances.

In the more recent literature, Brown and Earlam [12] cited the relation of prolonged immobilization and infection of the urinary tract. Long periods of immobilization were required in each of the six cases they report, although injury to the bone was not the primary cause in every instance. They stated that these diseases may be associated under any of the following three conditions: (1) when immobilization is required during the treatment of a noninfective lesion, as illustrated by the case reported by Cabot in 1910; (2) when calculous formation is accompanied by septic disease of a bone, as illustrated by the cases reported by Paul in 1923; (3) when calculous formation is accompanied by injury or disease of the spine, as illustrated by the cases reported by Müller in 1895.

Goldstein and Abeshouse [13] recently reviewed the literature on the association of urinary calculi and diseases of the bone and added fourteen cases. They pointed out the relationship between urinary lithiasis and various chronic diseases of the bone, such as osteomalacia and rickets, placing emphasis on the proper dietary management of patients with chronic diseases of the bone or injury to the bone.

Thus the literature on this subject is not extensive, and to a large extent it is confined to discussions of the association of the formation of calculi accompanying diseases of the bone, with brief consideration of the prevention of such complications. It is perhaps true that the presence of the calculi is often overlooked, as is illustrated by the few cases reported. Unless the possible presence of stones is considered, they may not be discovered, because it is well known that they may be present for years without producing pain or symptoms.

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9. Borman, M. C.: Bone Suppuration and Renal Calculi in Children, Am. J. Dis. Child. **40**:804-812 (Oct.) 1930.

10. Schwarz, O. A.: Fall von Bechterewscher Erkrankung mit doppelseitigen Nierensteinen, Ztschr. f. Urol. **24**:293-294, 1930.

11. Weber, W.: Steinbildung und Knochenerkrankungen, Ztschr. f. Urol. **25**: 36-41, 1931.

12. Brown, R. K. L., and Earlam, M. S. S.: Relation of Prolonged Immobilization and Urinary Tract Infection to Renal Calculus Formation, Australian & New Zealand J. Surg. **3**:157-171 (Oct.) 1933.

13. Goldstein, A. E., and Abeshouse, B. S.: Urinary Calculi in Bone Diseases: Review of the Literature and Report of Cases, Arch. Surg. **31**:943-981 (Dec.) 1935.

ETIOLOGIC FACTORS

The etiologic factors which are associated with the formation of urinary calculi may be classified in the following manner: (1) infection, both local and focal; (2) stasis; (3) hyperparathyroidism; (4) nutritional deficiency, and (5) phosphaturia.

When prolonged immobilization is required, as is usual in the cases of patients with orthopedic problems, several of these factors may be aggravated, such as stasis due to injury of the spinal cord, injury to the kidney, hypercalcemia and nutritional deficiency.

Infection and Stasis.—Many observers believe that infection is the major factor in the production of urinary calculi; however, this factor may be entirely absent in the presence of a renal calculus, as is illustrated by the case reported here. Likewise, it appears logical that in other instances the formation of stones may precede infection, which occurs later, either as a result of traumatization of the kidney by calculi or after stasis occurs owing to interference with the outflow of urine from the kidney. Certainly the factors which commonly are associated with the formation of calculi influence their formation in patients with orthopedic problems.

Bugbee [14] reviewed the results of operations for nephrolithiasis to determine the presence of preexisting pyelonephritis as a possible factor in the formation of renal calculi. A definite history of pyelonephritis was elicited in twenty-three cases. Treatment had been administered to seventeen patients during the initial attack, and in six the infection had been treated by other physicians. Although roentgenograms did not show the presence of a calculus when the patient was first seen, stones subsequently developed in all these patients. It is interesting to note that the urine was acid in reaction and that the colon bacillus was the offending organism during the first attack in sixteen cases; in nine of these the urine later became alkaline in reaction, and many staphylococci were present. In five cases the urine remained alkaline throughout the period of observation; in one it was neutral, and in another, both acid and alkaline reactions were noted during the period of observation. Calculi which formed in an acid urine were composed of calcium oxalate, and those which formed in alkaline urine were largely phosphatic in composition.

Keyser,[15] at the Mayo Clinic, reported obtaining positive cultures of the urine from the bladder of six of his twelve patients and a negative culture of the urine from one; culture of the urine of the five

14. Bugbee, H. O.: Recurring Pyelonephritis as Etiological Factor in Nephrolithiasis, Tr. Am. A. Genito-Urin. Surgeons **25**:121-131, 1932.

15. Keyser, L. D.: Relationship of Urinary Infections to Recurrent Calculi, J. Urol. **31**:219-238 (Feb.) 1934.

other patients was not reported. Paul [5] reported twenty cases in which renal calculi developed after suppuration of the bone due to war injuries. Subsequently, urinary infection was noted in 90 per cent of the cases, and Paul expressed the belief that urinary infection was the primary cause of calculous formation.

Barr and Charles [16] expressed the belief that infection, in common with stasis and an increase of calcium excretion in the urine, plays considerable part in the formation of stones. Northfield,[17] Weber,[11] Wallenstein [18] and others have cited the relationship of infection of the urinary tract and subsequent calculous formation after suppuration of the bone. In many of these cases there was injury to the spinal cord, with subsequent paralysis of the bladder and, after routine catheterization, cystitis developed, which later was followed by ascending renal infection.

Some authors have even recommended cystotomy in an effort to prevent such complications. Although calculi have been reported to develop in aseptic kidneys or in the presence of colon bacilli, this is not as frequent a finding as when urea-splitting organisms are present. Such organisms definitely contribute to calculous formation owing to the precipitation of the alkaline inorganic salts, such as phosphates and carbonates of calcium and magnesium. With this type of infection, calculi may develop with considerable rapidity, enlarge rapidly and eventually destroy the kidney.

Hyperparathyroidism.—Numerous studies have been made to demonstrate the relation between hyperparathyroidism and the formation of calculi, and the most important of these are the reports of Albright and Bloomberg,[19] Barney [20] and Chute.[21] Albright and Bloomberg reported twenty-three proved cases of hyperparathyroidism among which roentgen studies revealed the presence of renal calculi in fifteen. Laboratory examination showed a high level of serum calcium, a low level

16. Barr, D. P., and Charles, Cecil M.: Relation of Diseases of Bone to Arterial Calcification and Urolithiasis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, pp. 155-179.

17. Northfield, D. W. C.: Case of Fractured Pelvis Followed by Unusual Complications, Guy's Hosp. Rep. **83**:252-256 (April) 1933.

18. Wallenstein, S.: Renal Calculi Following Fracture of Spine, South. M. J. **24**:675-678 (Aug.) 1931.

19. Albright, F., and Bloomberg, E.: Hyperparathyroidism and Renal Disease with Note as to Formation of Calcium Casts in This Disease, Tr. Am. A. Genito-Urin. Surgeons **27**:195-202, 1934.

20. Barney, D.: Recurrent Renal Calculi, Surg., Gynec. & Obst. **35**:743-748 (Dec.) 1922.

21. Chute, R.: Vital Importance of Relation of Hyperparathyroidism to Formation of Certain Urinary Calculi—and Its Remedy, New England J. Med. **210**: 1251-1253 (June 14) 1934.

of serum phosphorus and an increase in the excretion of calcium and phosphorus in the urine. Disease of the bone without a coexisting renal pathologic process was present in only five cases in this series. These findings suggest that renal disease is a more frequent complication of hyperparathyroidism than is osseous disease.

In numerous cases renal colic has been reported as the presenting symptom leading to the diagnosis of hyperparathyroidism, which soon was associated with disease of the bone. Hunter and Turnbull [22] in 1931 reported the association of hyperparathyroidism and generalized osteitis fibrosa with renal calculi, and in several cases renal colic was the presenting symptom.

In our recent series of two hundred and ten cases in which complete studies of the blood have been made findings indicative of the presence of hyperparathyroidism were observed in only one instance, and this was verified by the removal of an adenoma of the parathyroid gland.

Vitamin A Deficiency.—Although a definite history of deficiency in the diet may not be elicited and although clinical evidence of such deficiency may not be well marked, one cannot be certain that a continuous mild degree of deficiency may not be present. Therefore, as a routine, we use the biophotometer test (for determination of the light threshold), which is the most accurate method available for estimating vitamin A deficiency in cases of renal calculi. In a recent clinical study of cases of nephrolithiasis, a positive reaction to the biophotometer test was obtained in thirty; questionable results were secured in four, and normal readings, in eleven. Jeans [23] recently found that 26 per cent of a rural group and 53 per cent of a village group of Iowa children presented evidence of vitamin A deficiency as judged by means of this test. In an urban group, the percentage was still higher, but in all except three of the children from the village and the rural district who remained under observation, normal dark adaptation developed after a period of ingestion of vitamin A or carotene. In one of our cases in which hyperparathyroidism was associated with bilateral renal calculi, we secured the lowest reading we have ever seen in any case of renal calculi, indicating that severe deficiency in vitamin A existed.

NUTRITIONAL DEFICIENCY

Several factors must be taken into consideration in determining the presence of nutritional deficiency. The seasonal influence of the

22. Hunter, Donald, and Turnbull, H. M.: Hyperparathyroidism, Generalized Osteitis Fibrosa with Observations upon Bones, Parathyroid Tumors, and Normal Parathyroid Glands, Brit. J. Surg. **19**:203-284 (Oct.) 1931.

23. Jeans, P. C., and Zentmire, Z.: The Prevalence of Vitamin A Deficiency Among Iowa Children, J. A. M. A. **106**:996-997 (March 21) 1936.

vitamin A content of dairy products and eggs has been cited in previous publications and has been well worked out by the Ohio Experimental Station. Likewise, in the so-called "stone areas" a definite deficiency in the diet has been shown to be present.

Vitamin A is essential to the diet because adequate amounts maintain the integrity of the epithelial structures, whereas when a deficiency in vitamin A exists, stratified epithelium is noted in the bladder, the ureters and the renal pelves. This may be followed by desquamation or ulceration of the mucosa of the renal pelves, and in the presence of strongly alkaline urine the phosphates and carbonates of calcium and phosphorus may adhere to the fibrin poured out from the denuded area. These small accumulations may be voided spontaneously, or they may gradually enlarge and drop into the dependent lower calix. Thus the initial calculus is formed, and further enlargement occurs as the phosphates and carbonates adhere to this nucleus. In the presence of acid urine, uric acid calculi may develop in like manner, while the oxalates are precipitated in a wide range of urinary reactions.

Phosphaturia.—Increased elimination of oxalates and uric acid in the urine as well as a persistent phosphaturia is associated with calculous formation. The urine may become alkaline temporarily, owing to the ingestion of an excess of alkaline ash food, or a temporary phosphaturia may be associated with a metabolic disorder. In either case an increase of phosphates in the total amount of body fluids is found. Likewise, disturbances in the function of the large bowel may produce a more permanent phosphaturia. Under such circumstances the usual amounts of earthy phosphates are not eliminated by the bowel, and a portion of the burden is shifted to the urinary tract. Phosphaturia in the presence of infections of a urea-splitting nature becomes an important factor in the formation of calculi. Such urine is found to be alkaline in reaction, and the phosphates and carbonates are precipitated rapidly, thus producing stones in a short time. Dietary control of the urinary reactions by changing the hydrogen ion concentration and eradication of the infection will minimize the formation of calculi.

ADDITIONAL ETIOLOGIC FACTORS

The factors just discussed are among those which commonly are seen in the presence of urolithiasis. In cases of coexisting disease of the bone of long standing, especially when injury to the vertebral column and subsequent pressure on the spinal cord take place or extensive suppurating wounds are found, additional factors may be responsible.

Injury to the Kidney.—Ofter a primary intrinsic lesion of the kidney occurs. Rupture of a considerable area of the renal tissue or even

of small vessels causes extravasation of blood into the renal pelves, and these blood clots serve as nuclei on which calculi may have their origin. Such intrinsic lesions may be slow to heal, and subsequent infection ascending from an inactive bladder constitutes a fertile field for the formation of calculi.

Holmes and Coplan [24] pointed out the importance of secondary or extrinsic injury of the urinary tract due to paralysis. Hollander [25] maintained that after an injury to the spinal cord there is an interruption of the reflex arc concerned in expression of the urine from the renal papillae into the pelvis, together with a loss of muscular activity of the bladder, ureter and pelves. This derangement of the entire upper part of the urinary tract favors urinary stasis and infection. Additional changes soon occur, such as decomposition and ammoniacal formation of urinary salts with the ultimate formation of phosphatic calculi.

Wallenstein [18] reported a case of crushing injury to the spine followed by paralysis. He expressed the belief that suprapubic cystotomy is indicated in such instances and that it is probably the best procedure for complete or incomplete transverse lesions of the cord, as both stasis and infections are eliminated.

Prolonged Immobilization and Stasis.—Extensive and chronic osteomyelitis, infected compound fractures, fractures of the spine and tuberculosis of the spine or hip require long periods of immobilization. As has been pointed out, such conditions are usually complicated by general infection, by infection of the urinary tract and stasis and by lack of essentials in nutrition (due to loss of appetite from inactivity) to such an extent that it is difficult to determine the primary factor in the formation of calculi.

The importance of prolonged immobilization and consequent stasis has been emphasized by Brown and Earlam,[12] who reviewed the literature and cited the relation between prolonged immobilization and the formation of renal calculi in six illustrative cases. They stated that urinary infection leads to accelerated growth of calculi but that this factor alone cannot be responsible for the formation of stones. The formation of calculi in the presence of noninfected lesions has been reported by Cabot [4] and Joly.[26] Brown and Earlam [12] pointed out that when a patient undergoes prolonged immobilization in the dorsal decubi-

24. Holmes, R. J., and Coplan, M. M.: Extensive Bilateral Renal Calculosis of Rapid Development Following Fracture of Vertebrae, South. M. J. **27**:228-233 (March) 1934.

25. Hollander, cited by Abeshouse, B. S., in discussion on Holmes and Coplan,[24] p. 232.

26. Joly, J. Swift: Stone and Calculous Disease of the Urinary Organs, St. Louis, C. V. Mosby Company, 1929, pp. 85-87.

tus position, the minor calices occupy the most dependent position, while the pelvis is drained at its highest point. In the majority of instances no harm is done if infection is not present, the physical condition of the urine being such that crystals are not deposited. In a patient, however, in whom deposition of crystals occasionally occurs and in whom crystals normally would pass from time to time, stasis in the minor calices can easily constitute the additional factor necessary for the production of calculi.

Prolonged immobilization, by interfering with drainage from the pelvis and calices, may provide sufficient time for a change in hydrogen ion concentration of the urine to take place and for the precipitation of crystals which ordinarily would not occur. We know that precipitation of carbonates and phosphates occurs only in an alkaline urine. This is true also of the precipitation of uric acid crystals which occurs when the hydrogen ion concentration is shifted strongly to the acid side.

HYPERCALCEMIA

After vertebral injury and accompanying paralysis, the formation of calculi composed of calcium has been attributed to demineralization of the bones and muscular inactivity during immobilization.

Hyperparathyroidism is characterized by marked hypercalcemia, and the calcium output in the urine is much greater than normal. In many cases in which no disturbances of the parathyroid glands are demonstrable but in which muscular inactivity and osseous destruction and reconstruction occur, a marked increase in the calcium content of the blood is found. Schwarz,[10] Barr and Charles [16] and Holmes and Coplan [24] pointed out the significance of this fact. Normally, about 90 per cent of the calcium taken into the body is excreted through the intestinal tract and 10 per cent through the urinary tract. These percentages vary markedly, however, and it is well known that the rates may be reversed easily, the greatest burden being placed on the kidney. However, it is probably true that the destructive and constructive processes in the bone will be affected by the consequent increase of calcium in the circulating blood and a greater excretion of salts in the urine. Roentgen examination reveals the degree to which decalcification of bone may occur during complete immobilization for a long time. Usually, general infection, infection of the urinary tract and malnutrition are also present, so that no single factor can be held responsible for the abnormal deposit of calcium.

CHEMICAL COMPOSITION OF CALCULI

In reviewing the literature, it is noted that a chemical analysis of the calculi has been made in only a few cases. However, the stones that have been analyzed have been found to be composed chiefly of calcium

phosphate. In one case reported by Brown and Earlam [12] the calculus was composed chiefly of calcium phosphate, but traces of calcium oxalate were also present.

In the series of twenty cases reported by Paul [5] calcium oxalate was the principal constituent in two instances, but the chemical constituents were not reported in the others. Brown and Earlam,[12] Taterka,[7] Borman,[9] Weber [11] and Holmes and Coplan [24] found calculi to be composed of calcium phosphate. In the four cases of calculi associated with fractures which I have seen in the past year, calcium phosphate was the principal constituent of the stones. Thus, it is apparent that the majority of the calculi which develop in patients with orthopedic problems are formed in the presence of an alkaline urine. Goldstein and Abeshouse [13] reported that chemical analyses showed that the stones in one of their cases were of mixed phosphatic type.

TYPE OF INFECTION PRESENT

Cultures have not been made of the organisms which have been present in the genito-urinary tract in most of the cases reported in the literature, and little mention is made as to whether the organism had the urea-splitting property. In case 4 cited by Brown and Earlam [12] an infection due to Proteus was present, and in case 6 Staph. albus was the offending organism. In the series of cases reported by Paul [5] the most common organisms were Staph. aureus and B. coli. In our series of six cases Proteus was cultured in two instances; Staph. aureus was present in one case, Proteus ammoniae in two and Bacillus Thompsoni in one. In four of the six cases the organism had the property of splitting urea strongly, and in one case this occurred but faintly.

SYMPTOMS AND DIAGNOSIS

When an orthopedic condition has existed for a long time, the diagnosis of complicating urinary calculi presents a greater problem than in the usual case of urolithiasis, because attention is directed largely to the major orthopedic problem with its usual complications. The patient is immobilized, and, owing to the inactivity, symptoms of renal calculi do not present themselves as early as they might in the active patient. An early diagnosis is important, since the formation of stones occurs more rapidly, and this means greater renal damage. The large number of contributing factors, such as hypercalcemia, immobilization and infection, which are associated in the majority of cases, also makes early diagnosis imperative, or, even better, the prevention of such complications should be sought.

In the cases reported in the literature, calculi were found as early as three weeks after immobilization. Holmes and Coplan [24] reported

that they had found stones four weeks after injury, and O'Conor [8] stated that he found bilateral renal calculi which developed within five months after injury and that during that time they had become so extensive that removal was impossible. In most instances diagnosis was made during the time of convalescence, but in a great number diagnosis was not made until after the patient became active.

Another reason why diagnosis is delayed is the fact that accompanying urinary infection and often urinary retention due to paralysis tend to obscure early signs of calculi. Burning, pyuria and perhaps frequency of urination, which are commonly associated with calculi, are already present. With severe infections, at least microscopic if not gross, hematuria may be found. In the cases reported hematuria was the most frequent presenting symptom, and this finding prompted many of the physicians to make a roentgen study which revealed the calculi. The third reason why the diagnosis of calculi is delayed in vertebral and pelvic injuries is that one tends to associate any accompanying renal colic with the pain due to the injury rather than with pain due to the complication. Renal colic was the second most common presenting symptom which suggested roentgen study in the cases reported. In many cases, however, calculi were so large that they were more or less fixed and little colic occurred. In other cases calculi were discovered accidentally during the course of roentgen examination. When calculi were found to be present after immobilization, renal colic, hematuria and passing of small stones or gravel were the presenting symptoms.

TREATMENT

When calculi are first noted, they may be producing an obstruction and destroying the renal parenchyma so that surgical intervention is essential to prevent complete destruction of the kidney. In other instances the calculi, when first discovered, may already have destroyed the kidney, and a marked infection may be present which requires nephrectomy. Our problem, therefore, is to prevent or minimize calculous formation which occurs during the long period of immobilization.

In reviewing the cases that have been reported in the literature and those that we have seen at the clinic, we are immediately impressed with the number in which alkaline urine was present during the period of immobilization. Therefore, the calculi which formed should consist of salts precipitated in a urine with a p_H on the alkaline side. This is true, and in cases in which chemical analyses were made, calcium phosphate was the chief chemical constituent. In two cases traces of calcium oxalate were also present. In order to prevent the formation of stones, we believe that patients suffering from fractures or osteomyelitis in whom a long period of immobilization is required should be placed on a dietary regimen in addition to other therapeutic procedures during this period.

PREVENTION AND TREATMENT OF INFECTION

Whether or not drainage should be instituted by means of a catheter after injuries to the spine is still a controversial subject. Personally, we believe that, if possible, spontaneous development of overflow is preferable. When drainage is instituted with a catheter, however, extreme care must be taken to minimize infection of the bladder which may result in subsequent renal infection. Catheterization under sterile precautions, irrigations of the bladder with a solution of potassium permanganate (1:4,000) and instillations of mild silver protein will help to prevent this complication. Likewise, urinary antiseptics, preferably sodium dihydrogen phosphate and methenamine, which render the urine acid in reaction, should be administered by mouth in large doses to aid in the eradication of the infection. The use of alkaline therapy should not be employed for any length of time. Careful examination of the urine at frequent intervals is essential to ascertain the number of pus cells in the urine, the type of organism present and whether precipitation of phosphates and carbonates is occurring.

The prevention of infection of the kidneys and the minimization of infection in the bladder cannot be emphasized too greatly. If the patient is maintained in a recumbent position, the position should be changed frequently if it is at all possible. Obviously, in cases of fracture of the pelvis or spine this may not be possible, but in cases of injury or infection of the leg such a shift in position may be feasible. Finally, by use of the high vitamin A acid ash diet, the p_H of the urine is shifted to the acid side to a level of 5 or 5.2, at which point the phosphates and carbonates of calcium and magnesium are held in complete solution, and precipitation of these salts does not occur. Vitamin A is administered in the form of two capsules of halibut liver oil or carotene in oil daily. Vitamin A is prescribed (1) for its effect in maintaining the integrity of the epithelium of the genito-urinary tract, (2) for the correction of vitamin A deficiency, if present, or the prevention of its development, and (3) for increasing the resistance of the patient to infection.

Obviously, in this group of patients a specimen of urine cannot be taken from the kidneys, and we must rely on the p_H of the urine from the bladder as a guide to the excess of acid ash to be included in the diet. In the absence of a urea-splitting infection in the kidney, the p_H of the urine from the bladder will usually suffice. The basic diet consists of an excess acid ash of 17.3 cc., which is varied daily according to the p_H of the urine.

The purpose of this diet is to furnish an adequate high vitamin diet in which the total acid ash exceeds the total basic ash. To accom-

plish this, it is absolutely necessary that no salt be used for seasoning foods, either in cooking or at the table.

The following foods, in the amounts designated, must be included in the diet daily.

A. Acid Ash Foods (Minimum Amounts):

1. Cereal—any one of the following measured servings (2 cc. excess acid ash):

	Amount
Cornflakes	1 cup heaping
Cornmeal (cooked)	⅔ cup
Farina (cooked)	⅔ cup
Oatmeal (cooked)	½ cup
Puffed wheat	1 cup scant
Puffed rice	1 cup heaping
Rice (cooked)	½ cup scant
Shredded wheat	½ biscuit

2. Meat—any two of the following measured servings (12 cc. each):

	Amount
Beef, loin, medium fat	4 by 4¼ by ½ inch
Chicken, broiled	One-half
Chicken, stewed	Breast or thigh plus leg
Cheese, cheddar	3½ by 2 by 1 inch
Codfish, fresh, cooked	¼ cup
Eggs	2
Frankfurters, large	2
Halibut	4 by 2 by 1 inch
Ham, fresh	4½ by 3 by ¼ inch
Heart, beef	2½ by 3 by 1 inch
Kidney, veal	¾ cup
Lamb chop	3 medium size
Lamb roast	5 by 5 by ¼ inch
Liver, beef	3 by 6½ by ½ inch
Mackerel, fresh	2 by 4 by 1 inch
Oysters, very large	3
Pork chop, thick	1
Salmon, fresh	3 by 4 by ¾ inch
Salmon, canned	½ cup packed
Trout	2½ by 3 by 1 inch
Turkey, 2 slices	2 by 3 by ¼ inch
Veal chop	1
Veal roast	3 by 2½ by ⅛ inch
White fish	2¼ by 3 by 1 inch

3. Bread—whole wheat—5 slices (2.2 cc. each)

4. Eggs—two (5.5 cc. each)

5 Miscellaneous—any one of the following measured servings (2 cc.):

Macaroni	¾ cup
Spaghetti	½ cup
Rice	½ cup
Corn	½ cup
Plain cake	1¾ by 1¾ by 1¼ inches

B. Alkaline Ash Foods (Maximum Amounts):

1. Milk—1 pint (7.2 cc.)
2. Cream—¼ cup (0.3 cc.)
3. Fruits and Vegetables—list to be given later (excess of basic ash not to exceed 25 cc.)

C. Concentrated Vitamin Foods:

1. Yeast—2 cakes
2. Cod liver oil—2 tablespoons; or halibut liver oil, 2 capsules before each meal
3. Wheat germ—2 tablespoons to be added to cereal

Fruits and vegetables shall be chosen from the following lists only. Any combination of fruits and vegetables may be selected, but the total excess basic ash in the selected combination must not exceed 25 cc. daily.

Fruit	Amount	Cc. of Excess Basic Ash
Watermelon	2½ by 2½ by ½ inch	2.7
Grapes	½ cup or 24 grapes	2.7
Pear	1 medium	3.6
Apple	1 small	3.7
Grape juice	½ cup	3.9
Lemon juice	½ cup	4.1
Cherry juice	½ cup	4.4
Orange juice	½ cup	4.5
Raspberry juice	½ cup	4.9
Peach	1 medium	5.0
Lemon	1 medium	5.5
Banana	¾ cup or ½ large	5.6
Orange	1 medium	5.6
Cherries	⅔ cup	6.1
Apricots	2 medium	6.8
Pineapple	⅔ cup diced	6.8
Muskmelon	½ cup	7.5
Rhubarb	½ cup	8.6

Vegetable	Amount	Cc. of Excess Basic Ash
Asparagus	½ cup	0.8
Green peas	¾ cup	1.3
Onions	½ cup	1.5
Pumpkin	½ cup cooked	1.5
Turnips	½ cup cooked	2.7

Vegetable	Amount	Cc. of Excess Basic Ash
Squash	½ cup mashed	2.8
Radishes	10	2.9
Mushrooms	½ cup canned	4.0
Cauliflower	⅔ cup cooked	5.3
String beans	⅔ cup cooked	5.4
Tomatoes	½ cup	5.6
Cabbage	⅔ cup cooked; 1½ raw	6.0
Tomato juice	½ cup	6.2
Sweet potato	½ medium size	6.7
White potato	1 potato 2½ inches diameter	7.0
Lettuce	¼ head or 16 leaves	7.4
Celery	4 stalks or ¾ cup	7.8
Cucumber	⅓ cup sliced	7.9
Rutabagas	½ cup mashed	8.5
Carrots	5.8 cup	10.8
Beets	⅔ cup	10.9

Note.—A few samples of permitted fruit and vegetable combinations, with the cubic centimeters of excess basic ash, are:

Orange juice, ½ cup	4.5	Apple, one	3.7	Muskmelon, ½ cup	7.5
Grapes, 24	2.7	Pineapple, ⅔ cup	6.8	Apple sauce, 1 apple	3.7
Cauliflower, ⅔ cup	5.3	Peas, ¾ cup	1.3	Tomato, ½ cup	5.6
Tomato, ½ cup	5.6	Cabbage, ¼ cup raw	3.0	Asparagus, ½ cup	0.8
Potato, 1 medium	7.0	Potato, one	7.0	Lettuce, ¼ head	7.4
Totals	25.1		21.8		25.0

In addition, the following acid and neutral foods may be used as desired:

Acid Foods	Neutral Foods
Cranberries	Sweet butter
Flour	Candy—no chocolate bars
Plain cookies	Cornstarch
Pastry with custard or allowed amounts of fruit fillings	Lard
	Olive oil
	Salad oil
English walnuts	Mayonnaise
Popcorn, no salt	Sugar
Unsalted peanuts	Tapioca
Unsalted crackers	Tea
	Coffee or Kaffee Hag
	Postum

The following list contains a few striking examples of foods which must be omitted because of their extremely high basic ash content.

Almonds	Olives
Beet greens	Parsnips
Dandelion greens	Raisins
Figs	Spinach
Molasses	Dried fruits and vegetables

Suggested Plan of Menu	*Sample Menu*
Breakfast:	
Fruit	Grapes
Cereal and wheat germ	Oatmeal and 2 tablespoons wheat germ
Eggs, two	Scrambled eggs
Bread, whole wheat	Toast, whole wheat, 2 slices
Salt-free butter	Butter, 2 squares
Milk	Milk, ½ pint
Cream	Cream, ¼ cup
Sugar	Sugar
Beverage	Coffee
Lunch:	
Meat	Veal chop
Rice or substitute (see miscellaneous)	Steamed rice
Vegetable or salad	Sliced tomatoes
Fruit	Baked apple
Bread, whole wheat	Whole wheat bread, 1½ slices
Salt-free butter	Butter, 2 squares
Beverage	Milk, 1 glass
Dinner:	
Meat	Roast beef
Vegetable	Potato
Vegetable or salad	String beans
Dessert	Tapioca cream pudding
Bread, whole wheat	Whole wheat bread, 1½ slices
Salt-free butter	Butter, 2 squares
Cream	Cream
Sugar	Sugar
Beverage	Coffee

Note.—One pint of milk is to be used each day, in any form.

In the absence of infection, an excess of 25 cc. of acid ash in the diet usually suffices to reduce the p_H of the urine to 5 or 5.2. When an infection is present, the acid ash content may be increased, and acidifying agents, such as ammonium chloride in enteric coated pills, may be used in addition to the diet. The diet is well balanced in all

respects aside from the excess of acid ash. The specimen of urine from the bladder should be secured at least three times weekly, and the sediment should be studied for crystals and for the type of precipitate which is present. Likewise, culture of the urine, determination of the p_H and stained smear of the sediment should be made. If crystals or sediments which precipitate in an acid urine are present while the patient is on the acid ash diet, the excess acid ash in the diet should be reduced to the point at which this precipitation does not occur. Thus, each patient must be individualized, and the diet varied according to the p_H of the urine and type of crystals that are precipitated.

CONCLUSIONS

The development of renal calculi in patients with orthopedic problems, in whom prolonged immobilization is necessary, is not as rare as we are led to believe from reports in the literature.

Measures to prevent infection of the genito-urinary tract should be employed constantly.

Frequent examination of the urine should be done while the patient is being treated.

Shifting the p_H of the urine to the acid side to a level of from 5 to 5.2, where precipitation of the alkaline salts does not occur, is of aid in minimizing the formation of the types of calculi reported in the literature.

The high vitamin A acid ash diet is of value in securing the desired p_H of the urine and preventing precipitation of phosphates and carbonates of calcium and magnesium, which are the chemical constituents of the calculi which develop in these patients. Likewise, by the use of this diet, we are able to maintain the patients on a well balanced diet during the period of immobilization.

A roentgenogram should be taken before the patient leaves the hospital, to rule out the possibility of a silent renal calculus.

PHLEGMON OF THE COLON

REPORT OF A CASE

JOHN BURKE, M.D.
BUFFALO

The gastro-intestinal tract is subject to every sort of inflammatory process, ranging in severity from a simple catarrhal type to a definite phlegmon. As in other organ systems, the milder types of inflammation are overwhelmingly more frequent. Among the least frequent types of lesion is the phlegmon. It was first described by Sand in 1700.

Phlegmon is found with a frequency which decreases in almost inverse proportion to the distance of its site from the stomach. Finsterer in 1928 collected from the literature and from his own records reports of two hundred and ninety-six cases of phlegmon of the stomach. There has been no definitive study of phlegmon of the small intestine in recent years comparable with Finsterer's monograph. However, it was necessary for me to review most of the reported cases while searching for those of phlegmon of the colon, and it is my impression that there are about one hundred cases of phlegmon of the small bowel reported. Goldschmidt reported the first case involving the large intestine in 1887, and since that time about fifty cases have been reported. The word "about" is used advisedly, as I am not at all certain that I have been able to find all of the reported cases. Some of the cases herein abstracted were found by chance, having been reported under titles considerably remote from "phlegmon of the colon." Of these cases I am presenting twenty-seven as representing "pure" phlegmon of the large intestine, at least to the extent that they do not appear to represent the spread of infection from an adjacent inflamed appendix or diverticulum. Fenkner has reported many examples of this lesion which I have not included because the accompanying data have been too meager for analysis. It is perhaps appropriate at this time to say that Fenkner considered this lesion as occurring frequently in milder forms, running its course undiscovered. He expressed the belief that the thin veil-like adhesions often found attached to the cecum and ascending colon are the end-result of a healed phlegmon, and he (in his article published in 1925) gave rather interesting evidence in support of his hypothesis. Most of the authors are not of his opinion, that the resulting stenosis will eventually require operation.

Abstracts of the reported cases, together with my case, follow.

CASES FROM THE LITERATURE

GOLDSCHMIDT'S CASE, 1887.—A woman aged 41 had been ill six days. Her temperature was 39.6 C. (103.3 F.). She had bronchopneumonia and abdominal distention on admission to the hospital. Vomiting and abdominal pain developed two days later. Death occurred thirteen days after the onset. Postmortem examination showed bilateral bronchopneumonia. The small and large intestine (limit not stated) were swollen and discolored, with a thickened wall showing the picture of an acute inflammatory process. No microscopic studies were mentioned.

DOWD'S CASE, 1912.—A man aged 23 was taken ill two and one-half days before admission to the hospital, with severe abdominal pain, nausea and bloody diarrhea. On admission he showed prostration and spasm of the left rectus muscle. The temperature was 98 F. At operation the colon from the sigmoid to the hepatic flexture was angry red, swollen and thick-walled. It was resected, and the patient recovered. Histologic examination showed infiltration of all the coats with leukocytes, lymphocytes and plasma cells. A purulent exudate was found on the mucosa. The reaction was most marked in the submucosa. Streptococci were found in the submucosa.

MÜLLER'S CASE, 1914.—A man aged 51 was seized with a sudden pain in the right side of the abdomen. Examination showed abdominal distention and diffuse tenderness, most marked at MacBurney's point. A diagnosis of perityphlitis was made. At operation the appendix was found to be anemic, and there was much turbid exudate in the pelvis. (The surgeon made a note of the discrepancy between the appendix and the exudate.) The patient died the following day with signs of peritonitis. At postmortem examination 400 cc. of thick red-yellow fluid was found in the abdomen. The colon and small bowel were dirty brown and edematous. The serosa was covered with a gelatinous coagulum for 20 cm. on the cecum and 25 cm. on the ileum. Microscopic examination showed that the most marked changes were in the submucosa. There were polymorphonuclear infiltration, areas of necrosis, marked interstitial edema and masses of streptococci and gram-positive bacilli in the tissues. There was a thin deposit of fibrin on the serosa, and streptococci were found in all coats.

VON SAAR'S CASE, 1915.—A youth aged 21 complained of a pain about the navel the day before admission to the hospital. Vomiting and an increase in the pain brought the patient to the clinic. On examination muscular spasms were found over the entire abdomen, with a maximal pain between MacBurney's point and the costal margin. The patient was operated on for acute appendicitis. The cecum to the hepatic flexure was thick and edematous, "like a stiff tube." There were bluish areas between the haustra. The appendices epiploicae were swollen. There was turbid fluid in the abdomen. The appendix was grossly normal. The bowel was exteriorized, and colostomy was performed. At a later date ileotransversostomy was performed, with recovery. Microscopic examination was not done.

HELLSTROM'S CASE, 1919.—A man aged 37 had tenesmus and bloody diarrhea for a short time. The night before admission to the hospital he collapsed with an abdominal pain and vomiting. He was acutely ill, with marked tenderness in both iliac regions and about the navel. The abdomen was explored through an incision in the epigastrium and in the right lower quadrant. The result of the exploration was negative. The patient continued to have pain in the left side and bloody diarrhea. He was reoperated on on the third day after the first operation. The descending pelvic and sigmoid colon were bluish red and thick walled; the mesosigmoid was inflamed. The extent of the lesion made resection inadvisable. The left kidney was explored because of persistent anuria. Death occurred

five days after the onset of the illness. Postmortem examination of the bowel from the splenic flexure down revealed the same picture as that noted at operation. The mesosigmoid and retroperitoneum were edematous. On microscopic examination the mucosa was found to resemble the état mammellonné of the stomach, due to the swelling of the wall. The process seemed localized in the submucosa. There was marked edema, with deposition of fibrin and swollen and broken-down cells. Many streptococci and gram-positive bacilli were seen, some in clumps.

BIEDERMANN'S CASE, 1921.—A woman aged 28 was taken with a sudden severe pain, like a labor pain. She did not pass a stool or flatus. The next day the pain localized in the right lower quadrant of the abdomen. She was admitted to the hospital on the second day. The temperature was 38.2 C. (100.7 F.). She was acutely ill, and her abdomen was slightly distended, with some spasm and tenderness in the right lower quadrant. The operation was performed the same day. The entire cecum was found to be acutely inflamed, bluish red and swollen, and the walls were of the consistency of belt leather. Ileocecal resection was performed, with recovery. Pathologic examination showed no break in the mucosa. The submucosa was chiefly involved, being infiltrated with leukocytes, lymphocytes and plasma cells. The mucosa was brownish, glossy and edematous. Bacterial stains were negative.

LEUCHTENBERGER'S CASE, 1923.—A woman aged 50, six months before her present illness, had an attack of jaundice, vomiting and diarrhea. In February 1923 she was again ill with fever and pain in the right side. Jaundice developed, with chills and eventually coma. Examination showed a jaundiced comatose woman with fever. There was dulness at the base of the right lung. Pleural puncture showed yellowish fluid, which contained leukocytes and erythrocytes. The skin of the abdomen was glossy, and the epigastric veins were prominent and tortuous. Ascites was present. There was pain on deep pressure in the right side of the abdomen, which was not localized. A blood culture was positive for pneumococci. The stool was acholic. The patient died fifteen hours after admission to the hospital. According to the report of the autopsy, the entire large bowel was relaxed, heavy and shapeless. The mucosal folds were changed into thick gelatinous protrusions. The wall was enormously thickened and brawny. Histologic investigation showed that the process involved chiefly submucosa. Pneumococcus lanceolatus was recovered from tissue in the culture and was demonstrated in section. The postmortem diagnosis was Laënnec's cirrhosis, gastritis and chronic catarrhal enterocolitis, pseudomelanosis, beginning phlegmon of the cecum and the ascending colon, paranephritic abscess on the right, abscess of the adrenal gland on the right, partly purulent ascites, calculus of the common bile duct, icterus and partial atelectasis.

SAUER'S CASE, 1923.—A boy aged 16 for seven days had pain in the right lower quadrant of the abdomen and fever and vomiting, with normal bowel movements. On admission to the hospital he was acutely ill, with a dry and coated tongue but a normal temperature. There was slight distention of the upper part of the abdomen. At operation the cecum as far as the hepatic flexure was found to be blue-red, swollen and edematous and covered with a fibrinopurulent exudate. Ileocecal resection was performed. Death occurred the following day. On pathologic examination the appendix was not remarkable. The serosa of the cecum was found to be covered with fibrin. There were walnut-like projection of mucosa into the lumen, which admitted about one finger. There was marked infiltration of all coats with leukocytes, which was most marked in the submucosa. Tricocephala were found in the mucosa, but there was no evidence of penetration into the deeper layers.

FENKNER'S CASE, 1925.—Robert M. was admitted to the hospital because of appendicitis, with severe pain and vomiting and a temperature of 38 C. (100 F.). The point of tenderness was very high in the region of the gallbladder. The patient requested immediate operation because of the pain. The appendix was free from inflammation as was the cecum, though the latter showed the veil-like signs of an old process. "The entire transverse colon was in a freshly inflamed condition such as I have previously described, that is, covered by a fresh, red, brawny membrane."

TEUTSCHLAENDER AND VALENTIN'S CASE, 1925.—A woman aged 51 had typhus at the age of 35. Eight days before admission to the hospital she had headache, fever and fatigue. There were no gastro-intestinal symptoms until the day of admission, when there was severe pain in the right lower quadrant of the abdomen, but no vomiting. The patient's condition was diagnosed as acute appendicitis and she was hospitalized. In the right lower quadrant of the abdomen at MacBurney's point and toward the crest of the ileum there was a broad and very sensitive area of resistance, about the width of a hand. A diagnosis of an inflammatory lesion in the cecum was made. Appendicitis was considered improbable. A pararectal incision was made. The omentum was found to be lightly injected. On the contrary, the cecum at the junction of the ileum was brawny and edematous. Ileocecal resection was performed. The mucosa was loosely attached but macroscopically was uninvolved. The submucosa was chiefly involved. According to the record the condition was phlegmon of the individual coats of the cecum around the junction of the ileum, which had not spread widely.

BUNDSCHUH AND WOLFF'S CASE, 1925.—A woman aged 31 for two days had pain in the lower part of the abdomen, with nausea. Her condition was diagnosed as acute appendicitis, and she was admitted to the hospital. The right lower abdominal quadrant was spastic and painful. The temperature was 38 C. The cecum was swollen, red and edematous, extending for about 6 cm. toward the ascending colon without a very sharp border. To a lesser extent, from 2 to 3 cm. of the ileum and the appendix were also involved. Ileocecal resection was performed, with recovery. The pathologic diagnosis was phlegmon of the cecum.

DOBERAUER'S CASE, 1926.—During an attack of erysipelas, Doberauer had severe pain in the right side of the abdomen. A diagnosis of mesenteric thrombosis was made. At operation the cecum and the ascending colon and one half of the transverse colon were found to be very red and succulent, with an extremely edematous wall. Cecostomy was performed. When an attempt was made to close the cecostomy opening, peritonitis developed, but the patient eventually recovered.

MOLL'S CASE, 1926.—A youth aged 21 for nine months before admission to the hospital had had occasional abdominal pain and for four days before, severe pain, diarrhea and vomiting. He showed the hippocratic facies, a boardlike condition of the abdomen on the right side and a temperature of 38 C. The maximum tenderness was in the right lower quadrant. At operation the cecum and terminal portion of the ileum were found to be inflamed and thickened and covered with fibrinous exudate. The appendix was involved to a lesser degree. Ileocecal resection was performed, with recovery. The mucosa of the specimen resembled tuberculous ulceration. The histologic diagnosis was phlegmon of the cecum.

MOLL'S CASE, 1926.—A man aged 30 complained of abdominal pain for a number of days. There was spasm of the entire right rectus muscle and marked tenderness over MacBurney's point. At operation the cecum was found to be inflamed and hard. One area was somewhat soft and was covered with fibrinous

exudate. The mesentery was inflamed. Ileocecal resection was performed, with recovery. The specimen when cut showed an ulcer resembling a peptic ulcer, underlying the exudate. There was no evidence of cancer or tuberculosis. (Note by Moll: Through error the ulcer was not studied further.)

FENKNER'S CASE, 1927.—In this case a clinical diagnosis of appendicitis was made. At operation the appendix was found to be slightly reddened. The cecum for from 8 to 10 cm. was deep red, stiff and swollen and covered with inflammatory exudate. Recovery followed without further operation.

FENKNER'S CASE, 1927.—The paitent in this case suffered from severe pain and vomiting and had a temperature of 38 C. The pain was high, almost in the region of the gallbladder. A diagnosis of appendicitis was made. At operation the appendix and cecum were found to be normal. All the intestines were in the pelvis and were adherent, with a fresh exudate. There was free pus in the pelvis. There was an inflammatory process in the sigmoid colon, as in the cases previously described. The pelvis was drained with a glass tube. Three days later a fecal fistula developed 10 cm. from the anus. Cecostomy was performed later. An abscess developed about the sigmoid colon. Recovery occurred after closure of the fistula and the cecostomy opening.

FENKNER'S CASE, 1927.—In this case the patient's condition was diagnosed as acute appendicitis. At operation the appendix was found to be normal. The cecum was red and swollen, and there was an edematous area the size of a quarter above its base. Appendectomy was performed, and cure resulted.

FENKNER'S CASE.—This case is similar to the preceding one. Local resection of the involved area was performed. The wall was 1 cm. thick; the mucosa was intact. The remainder of the wall was phlegmonous and necrotic. The appendix was normal.

OTTO'S CASE, 1927.—A man aged 28 was admitted to the hospital with a fecal fistula and an appendectomy scar. The report from the first surgeon showed that the patient had been admitted to the hospital with a complaint of severe pain radiating upward from the navel and signs of acute appendicitis. Operation was performed on Nov. 11, 1922, at which time the cecum was found to be long and mobile, and markedly inflamed, with fibrinous exudate on the serosa for half the length of the cecum. Appendectomy was performed approximately two years later. An abscess in this region was opened on May 5, 1926 (Otto). The fistula was repaired but broke down six days later. At the second operation the cecum was found to be as thick as a finger and covered with adhesions. Ileocolostomy and later ileocecal resection were performed. The specimen presented a picture of the end-result of a chronic inflammatory process.

FENKNER'S CASE, 1928.—A boy aged 12 had a tonsillar abscess, thrombosis of the corpora cavernosa penis, and thrombosis of both legs. After recovery there was sudden pain in the abdomen, with vomiting and prostration. There was a tumor in the right side, with spasm of the right rectus muscle. At operation the appendix was found to be normal. There was an invagination of the cecum 5 cm. from its origin to the transverse colon. Evagination was done. Three haustra were inflamed, bluish red and inverted. Two were restored to normal shape, but the third could not be so restored. Ileocecal resection was done, with recovery. The mucosa was normal, but there was a phlegmon in all other coats. The pathologic diagnosis (Breslau) was invagination on the basis of an inflammatory lesion of the cecum.

FINSTERER'S CASE, 1931.—A woman aged 29 for four months had fever, cramps and diarrhea, with a loss in weight of 38 Kg. There was a sausage-shaped tumor

in the right lower quadrant of the abdomen. The patient was operated on for ileocecal tuberculosis. Ileocecal resection was performed, with recovery. The pathologist, Paltouf, assumed that an acute phlegmonous process was present in the colon.

Bsteh's Case, 1932.—A man aged 22 had an attack of severe pain in the right lower quadrant of the abdomen and since then discomfort after each meal. Neither nausea nor fever was present. There was pain with defecation. A hard tumor the size of an apple was palpable in the right lower quadrant. Roentgen examination showed ulcerative induration of the wall of the cecum. The patient was observed for four weeks, during which time there were two ileus-like attacks. A diagnosis of ileocecal tuberculosis was made. At operation the cecum and the appendix were found to be markedly reddened, covered with fibrinous exudate and fixed to the retroperitoneum. Ileocecal resection was performed, with recovery. Histologic examination showed a small abscess in the submucosa near the origin of the appendix. All coats of the cecum showed marked inflammatory reaction with many leukocytes. Many gram-positive cocci were found throughout the sections.

Bsteh's Case, 1932.—A man aged 55 for months lost weight and appetite. For two weeks before admission to the hospital he did not have a bowel movement and suffered from marked distention. For the last three days he had cramplike pains throughout the abdomen, with nausea and belching. The abdomen was distended, with slight spasm and tenderness, which was more marked in the cecal region. The diagnosis was carcinoma. At operation the cecum was found to be distended, with severe changes in the wall. The serosa was bright red and covered with fibrinous exudate. There were occasional tears in the serosa. The ascending colon was free. The appendix was normal except for old adhesions. The cecum was exteriorized and opened by means of cautery two days later. Death followed. Postmortem examination showed a severe necrotizing inflammation of the cecum, with brawny edema of the mucosa and circumscribed fibrinopurulent peritonitis on the serosa.

Bseth's Case, 1932.—A woman aged 45 had a febrile angina. Seven days later there was marked pain in the right lower quadrant of the abdomen with vomiting, prostration and mild diarrhea. Examination revealed healing tonsillitis and diffuse bronchitis. The abdomen was somewhat distended. There was a high fever. A diagnosis was made of perityphlitic abscess. At operation the cecum was found to be adherent to the omentum and the anterior peritoneum. The appendix was embedded in the wall of the cecum. Appendectomy was not done. A tampon was placed to the affected area. The patient died. Postmortem examination showed the cecum to be thick walled and covered with fibrinopurulent exudate. On section the layers were clearly defined. The mucosa protruded and was covered with exudate. There was no evidence of trauma to the mucosa. The ileum was similarly involved in the region of the ileocecal valve. The appendix was uninvolved except in the serous layer. The cecum was involved for 10 cm. On histologic examination the submucosa and the mucosa were found to be tremendously edematous, the muscularis being the least involved. Few pus cells were seen. Colon bacilli were recovered from the bowel and colon bacilli and streptococci from the tonsils.

Szabó's Case, 1934.—A woman aged 41 a few weeks before admission to the hospital had severe pain in the region of the appendix. The pain disappeared after a time, and a tumor was felt. On admission, she showed pallor and emaciation. There was a mass in the right lumbar region the size of two fists, which was

mobile to respirations. There was also a mass in the region of the appendix the size of an apple, which moved with the first mass. The temperature was 38 C. There was leukocytosis. A roentgenogram showed the cecum to be compressed from without. An operation was performed in view of a diagnosis of disease of the gallbladder and appendicitis. The cecum was found buried in adhesions. It was thick walled, deep red and covered with a fibrinopurulent exudate. The appendix was involved to a minor degree. Ileocecal resection was performed, with recovery. The mucosa was somewhat injected. A few specimens of Oxyuris were present. Histologic examination showed the submucosa to be infiltrated with purulent material to a greater degree than the other coats. Oxyuris was present only on the surface of the mucosa.

DEMEL'S CASE, 1932.—A man aged 58 seven months before operation had pain in the left side of the abdomen, distention and a loss of 36 Kg. in weight. No blood or mucus was found in the stool. Roentgenograms showed a marked change in the wall of the sigmoid colon, which for about 5 cm. had become an irregular, stiff channel with a lumen the size of a finger. At operation a tumor was found in the sigmoid colon adherent to the lateral peritoneum and mesocolon, which produced stenosis. Exteriorization with subsequent resection was performed. The pathologic report (Morisch) stated that the picture was that of a phlegmonous inflammation of the large intestine. The patient recovered after the closure of a preternatural anus.

KONJETZNY'S CASE, 1935.—A woman aged 32 had a sudden pain in the right side of the abdomen and bloody diarrhea later in the same day. Hot compresses gave occasional relief. She was admitted to the hospital on the sixth day in poor condition. There was an old scar on the right side of the abdomen. Operation was performed for carcinoma of the sigmoid colon. The sigmoid and descending colon were covered by dense adhesions and were very thick walled. A Mikulicz resection was performed, with recovery. The pathologic examination revealed the picture of a phlegmon in a stage of regression.

AUTHOR'S CASE

A girl aged 18 four days before admission to the hospital began to have pain around the umbilicus and in the right lower quadrant of the abdomen. The pain gradually increased in severity but was somewhat alleviated by walking. There was no nausea or vomiting. Administration of a cathartic the day before hospitalization resulted in many loose bowel movements the following day. On the patient's admission to the Buffalo City Hospital the temperature was 100 F. and the pulse rate 84. The patient was well developed and well nourished and did not appear acutely ill. Pathologic changes were limited to the abdomen. There was no distention or spasm but marked tenderness over the right lower quadrant. There was some tenderness on palpation of the right fornix of the vagina.

There was an occasional red blood cell in the urine. There was a leukocyte count of 13,300, with 70 per cent polymorphonuclear leukocytes. A diagnosis of acute appendicitis was made.

A lower right rectus incision was made with the patient under spinal anesthesia. When the peritoneal cavity was opened no free fluid was found. The omentum presented into the wound. Palpation revealed what was thought to be a thickened retrocecal appendix. When the omentum was brushed away, a portion of it was intimately adherent to the cecum about 1 inch (2.5 cm.) above the ileocecal valve. This was left in place and cut free from the remaining omentum after double ligature. It was then seen that the supposed retrocecal appendix was, in fact, a

portion of the wall of the cecum. The cecum for about 3 inches (7.6 cm.) proximately was angry red, its serosa was rough and shaggy and its walls were markedly swollen and edematous. The remainder of the colon was normal in appearance. There was definite demarcation between the normal and the pathologic bowel. The appendix was uniformly fiery red and somewhat edematous. Its serosa was smooth and glistening, and it was nowhere adherent. The area underlying the omental adhesion on the cecum reminded one of the outline of a peptic ulcer. At the time of operation I was not acquainted with the subject of cecal phlegmon, and in view of the fact that the involved bowel did not seem to be tuberculous or carcinomatous and did seem to be an acute inflammatory process, ileocecal resection was not performed. Appendectomy was performed. The omentum was wrapped around the inflamed bowel, and the incision was closed in layers without drainage. At the time the postoperative diagnosis was acute perityphlitis and acute periappendicitis. Convalescence was uneventful, and on the eighth postoperative day the patient was discharged.

Histologic Examination (Dr. Jacobs).—The material as received consisted of an appendix with attached meso-appendix. It measured 7 cm. in length and 0.5 cm. in diameter. There was definite congestion of the serosa; otherwise the material did not appear remarkable.

Microscopically the serosa was found not only markedly congested but diffusely edematous. In the stroma there were numerous interstitial hemorrhages with scattered leukocytes. The vessels were engorged, and the intima was swollen. There were patches of edema and vacuolation in the inner circular layer of muscle. The germinal centers were large, and the rim of lymphocytes was thin and small. In the submucosa there was some adipose tissue. There were some desquamated mucosal cells mixed with cellular débris free in the lumen.

Bacteriologic cultures were not made. Sections were stained for bacteria by the methods of Gram and Giemsa. The serosa was carefully scrutinized for bacteria, and a few scattered gram-positive cocci, paired and in short chains, were found. Examination from the inside revealed a mixed bacterial flora in the débris among which gram-positive cocci in pairs and short chains could be readily picked up. Careful search, however, did not reveal any in the submucosa or in the muscle layers. This case shows more definitely a picture of acute periappendicitis, such as is frequently found in association with an inflammation of a contiguous structure.

PATHOLOGIC ANATOMY

The descriptions of the gross appearance of the acute lesions are strikingly similar. Demel's description is particularly apt: "Das befallene Darmstück sieht graurot bis dunkelblaurot aus, die Serosa ist mit Fibrinbeschlägen belegt, und der Darm selbst fühlt sich hart und teigig an." (The involved portion of the bowel varies from a grayish red to dark bluish red, the serosa is covered with a fibrinous exudate and the bowel itself feels firm and doughy.) The area involved may be a portion of a single haustrum or the entire diameter of the bowel for from 50 to 60 cm. There is, as a rule, a distinct demarcation from normal bowel. The degree of thickening of the intestinal wall is variable and may be so marked as to almost obliterate the lumen. A cross-section shows the reaction to be most marked in the submucosa, which is from ten to twenty times its normal thickness. The amount of swell-

ing in the submucosa sometimes causes a flat papillary protrusion of the mucosa. The mucosa is swollen and glossy and usually intact. Rarely it is ulcerated to a greater or lesser degree. There is edema of the serosa, which is nearly always covered, at least in part, with a shaggy, fibrinopurulent exudate.

HISTOLOGIC STRUCTURE

All layers of the intestinal wall take part in the inflammatory process. As a rule, the mucosa shows the least reaction. The serosa, the muscularis and the submucosa are involved, in the order of increasing severity. The predominant involvement of the submucosa is in keeping with the picture of phlegmon in other portions of the gastro-intestinal tract (Demel, Goldschmidt and Konjetzny). The submucosa is always very edematous. It is densely infiltrated by leukocytes, and there is an increase in lymphocytes and plasma cells. In several cases attention has been drawn to an increase in the proportion of eosinophils. Minute abscesses are sometimes found. The same type of inflammatory reaction is found in the other layers, but in lesser degree. The presence of a fibrinopurulent exudate on the serosal surface has been previously described.

BACTERIOLOGY

In those cases in which cultures have been taken or sections stained for the presence of bacteria, streptococci have been the most frequent invaders. Staphylococci, pneumococci, colon bacilli and putrefactive bacteria have also been demonstrated.

PATHOGENESIS

The portal of entry of infection is thought to be a defect in the mucosa, although this is seldom demonstrable. Fish bones and intestinal parasites have been found in the lumen of the bowel in some instances and have been considered as inciting agents by their discoverers. Fenkner contended that fecal stagnation plays a large rôle, considering infection of the blood stream as possible but unlikely. His experiments with skatole (Fenkner, 1925) are suggestive but do not seem particularly applicable to the disease as found in man. Doberauer, reporting his own case, stated definitely that he believed the phlegmon to be another manifestation of concurrent erysipelas. This seems entirely possible. Bsteh expressed the opinion that the angina which preceded the illness of one of his patients was definitely associated with the lesion in the bowel. The presence of intestinal parasites in the lumen of the bowel and in the mucosa may be significant in those cases in which it was reported (Sprengel; Teutschlaender and Valentin), but the lack of evidence of penetration beyond the mucosa weakens this point of view. The state-

ments of Sprengel and of Finsterer to the effect that the disease is definitely and necessarily associated with acute appendicitis have been thoroughly disproved. In all of the cases previously cited the appendix was uninvolved or involved secondarily by contiguity. It is true, however, that in many of the cases described in the literature as instances of phlegmon of the cecum the condition has been associated with perforative appendicitis.

DIAGNOSIS

As yet the disease has not been diagnosed preoperatively; in fact, the correct diagnosis was made by the pathologist as a rule. Acute appendicitis, carcinoma and tuberculosis have been the most common preoperative diagnoses. The symptomatology is extremely varied. Abdominal pain, usually referred to the overlying quadrant, was the symptom most consistently present. Fever was not remarkable. Constipation was common and diarrhea rare. A tumor was frequently present. Blood, pus or mucus in the stool was not a common finding. The leukocyte count was rarely mentioned. If the possibility of its occurrence is kept in mind, the diagnosis of phlegmon of the colon may on a fortuitous occasion be made preoperatively.

THERAPY

The treatment has been most frequently one or another of the types of resection. Fenkner, almost alone, has refrained from radical surgical measures, aside from the diagnostic laparotomy. In Doberauer's case cecostomy was performed, and in my case, appendectomy. It is my feeling that the treatment is of necessity surgical, because of the extreme uncertainty of diagnosis, both of the disease and of its severity. After a diagnosis has been made, the consideration of radical versus conservative treatment must be faced. It is true that Fenkner's mortality rate with simple exploration, with or without appendectomy, is by far the lowest of the reported series, but it is difficult to determine whether or not the lesions were of comparable severity. In the future I shall be inclined to do resection only in the presence of a predetermined stenosis. It is likely that a short-circuiting anastomosis would be as effective and probably less dangerous. It is well within the realm of possibility that the healing process without resection will cause sufficient scarring to require future resection or anastomosis to overcome obstruction. Anschutz and Konjetzny also are of this opinion.

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A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 564)

BLADDER

Tumor.—Wishard, Hamer and Mertz [37] stated that the malignancy of tumors of the bladder can be graded 1 in about 30 per cent of such cases. The most common type of growth on this organ is that which is on a broad, sessile, infiltrating base. A few vigorous endoscopic treatments have been found to give the best results if the tumor is not too large or too broad at the base. Suprapubic resection and electrocoagulation should be employed only if subsequent cystoscopy indicates that progress is unsatisfactory and provided the tumor is in a resectable region. With the modern prostatic electrotome, large masses of neoplastic tissue, which formerly required open operation, can be removed from the bladder. Open operations which necessitated massive electrocoagulation and application of radium were performed by the authors in about 30 per cent of cases of tumor of the bladder. Fifty per cent of the patients who had an open operation and destruction of the neoplasm

37. Wishard, W. N., Jr.; Hamer, H. G., and Mertz, H. O.: An Evaluation of Various Methods of Treating Tumors of the Bladder, J. Urol. **35**:503-506 (May) 1936.

with diathermy died within six months thereafter. Radium emanations have been used in approximately 10 per cent of the cases of vesical tumor. The grading of these tumors has varied from 1 to 4, and the size, from small growths, which were treated endoscopically, to large ones, which were treated by open operation. In 75 per cent of the cases in which radium was used, there were recurrences; in the remaining 25 per cent, the application of electrocoagulation alone would probably have given as satisfactory results. The inaccuracy of methods of application through the cystoscope has been the chief difficulty in the use of radium emanations. Applicators available for use through a suprapubic incision are more accurate.

Rabson [38] reported a case of leukoplakia and carcinoma of the urinary bladder, which supplements the reports of 125 cases of leukoplakia which have been published. Only 19 of these cases were associated with carcinoma and only 1 with sarcoma. Of these cases of uncomplicated leukoplakia in which age and sex were stated, 57 were in males and 14 in females. The maximal number of cases in the male occurred during the third decade and in females a decade later. Leukoplakia of the bladder was more common than elsewhere in the urinary tract.

The occurrence of cystitis with leukoplakia of the urinary bladder is emphasized by almost all authors, although in some cases it was definitely stated that cystitis was not present. Cystitis was stated to be present in 63 cases. Vesical calculus was reported in 12 cases. Comparison of the small number of cases of leukoplakia associated with calculi (14 per cent) to the number of persons with stones in the bladder diminishes the significance of the etiologic part played by stone as a cause of leukoplakia. There was a history of gonorrhea in only 10 cases. Syphilis was noted in 11 instances. Tuberculosis of the urinary tract was reported in only 1 case in which leukoplakia of the bladder was present.

Carcinoma associated with leukoplakia begins, according to the literature, about a decade after uncomplicated leukoplakia and reaches its height about two decades later. The base of the bladder, including the trigon and neck, was the most common site for leukoplakia. That area was mentioned in 19 cases as being the only portion of the bladder involved, or at least one of the areas included in the process. The right lateral wall was involved in 11 cases, the entire bladder in 9 cases and the anterior and posterior walls in 8 cases each. The superior wall was involved in 6 and the left lateral wall in 5 cases. The trigon was reported to be the most common site for epithelial neoplasms as well.

38. Rabson, S. M.: Leukoplakia and Carcinoma of the Urinary Bladder: Report of a Case with a Review of the Literature, J. Urol. **35**:321-341 (March) 1936.

In many of the cases reported, leukoplakia of the bladder was discovered at necropsy. In others, the patients died soon after the diagnosis was established or after operation.

Infection with Trichomonas.—Heckel [39] reported a study of the pathologic alterations in the female bladder and urethra that resulted from infection with Trichomonas vaginalis. Of the 43 females with this condition, the youngest patient was 17 and the oldest was 61 years of age. Twelve patients were single, and 31 were married. Eleven (25.5 per cent) of the total number of patients had had a miscarriage. Thirty-seven patients had had urinary symptoms at some time, and in many cases the acute urinary and gynecological symptoms had begun at the same time. In the cases in which urinary difficulties were present, cystoscopy revealed lesions of the bladder or urethra in 24 but did not disclose any abnormality in the remaining 13.

The gynecological symptoms noted were leukorrhea or vaginal discharge in 42 cases, abdominal pain in 14, backache in 12, metrorrhagia in 11, dysmenorrhea in 6 and itching in the region of the urethra in 11. Examination of the vagina revealed a "strawberry" appearance in 12 cases, senile changes in 2, acute vaginitis in 3 and bartholinian abscess in 2. The external orifice of the urethra usually will be found to be normal. In some cases pressure on the urethra will express a discharge, which will be found to contain Trichomonas. Cystoscopy will reveal that the pathologic changes in the bladder are limited almost entirely to its base, usually in the region of, and anterior to, the trigon. The following changes may be observed in the urethra: The internal orifice of the urethra, usually from 4 to 8 o'clock if visualized as the dial of a clock, is rough, boggy and gray; it may bleed easily. The mucous membrane of the urethra itself is in folds, which contain many small red patches.

Pieces of tissue were removed from the base of the bladder for biopsy, and sections were made. Marked change in the character of the epithelium was noted. Instead of the usual pseudocolumnar type of epithelium, part of each section was composed of large squamous epithelial cells which were closely packed together. At the surface, the mucosa was relatively normal in appearance, although there were some papillary protrusions near the surface. The sections in most instances were nodular, as if they represented the tops of superficial papillary projections. Analysis of catheterized specimens of urine revealed pyuria in 9 cases and hematuria in 6. In only 2 cases was Trichomonas found in the urine; urinary culture revealed streptococci in 9 cases. The diagnosis was based on the history, the demonstration of T. vaginalis in

39. Heckel, N. J.: A Study of the Pathologic Alterations in the Female Bladder and Urethra Resulting from Infection with Trichomonas Vaginalis, J. Urol. **35**:520-523 (May) 1936.

the sections from the vagina or urethra and the discovery of the lesions in the bladder or urethra. The differential diagnosis of this condition and other urinary diseases may at times be difficult; usually, if the cystoscopic picture reveals the findings which have been described, the diagnosis can be made, even if Trichomonas vaginalis cannot be recovered from the vaginal section at the first examination.

Neurogenic Dysfunction.—Creevy [40] stated that in most cases neurogenic dysfunction of the bladder is due to sensory lesions. Early in their course partial retention develops, which can often be relieved by rest of the bladder with the inlying catheter, supplemented by the administration of drugs to increase the expulsive force, provided the patient is trained to urinate at regular intervals. Later, the wall of the bladder is injured by the distention, so that some degree of atrophy occurs, and overflow incontinence follows. In selected cases, from six to twelve weeks of rest of the bladder by cystostomy, followed by careful training, may give relief. Regular urination must be maintained permanently if recurrence is to be avoided. With more severe injury to the detrusor muscles, cystostomy is preferably supplemented by presacral neurectomy, which should be regarded only as a means of increasing expulsive force. If the lesion of the nervous system is advanced enough to produce incontinence of the bowels, the prospect of cure by these methods is unfavorable, because sensation is insufficient to permit continuous voluntary contraction of the external sphincter.

Resection of the Neck of the Bladder.—May [41] described a case of sclerosis of the neck of the bladder of a woman aged 65 years; the condition was cured by transurethral resection.

PROSTATE GLAND

Hypertrophy.—Orr and Rue,[42] in a review of information obtained by a questionnaire concerning cases of prostatic obstruction, found that 73 surgeons had performed prostatic resections 14,104 times and prostatectomy 5,062 times during the same period of time. These totals reveal that resection is performed almost three times as often as is prostatectomy. There were also 214 operations on the neck of the bladder performed with Young's punch or similar punch instruments.

The total number of deaths following resection was reported to be 370, or 2.5 per cent, and from prostatectomy, 195, or 3.8 per cent.

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40. Creevy, C. D.: Treatment of the Overflow Incontinence of Neurogenic Vesical Dysfunction, J. Urol. **35**:507-514 (May) 1936.

41. May, Ferdinand: Ein Fall von Sphinctersklerose bei der Frau, Ztschr. f. urol. Chir. u. Gynäk. **42**:308-311 (Aug.) 1936.

42. Orr, L. M., II, and Rue, D. T.: Present Day Conceptions in the Management of Prostatic Obstruction, J. Florida M. A. **22**:573-578 (June) 1936.

There were 107 severe primary hemorrhages accompanying resection which necessitated opening the bladder. There were 164 secondary hemorrhages that required fulguration of the bleeding points, 116 that required transfusion and 54 that required both measures. Six hundred and forty-eight severe infections, or 4.9 per cent of all cases, were reported associated with resection.

Forty surgeons reserved the transurethral procedure for small glands only. Thirty-two employed it in all types of hypertrophy. Secondary resection was necessary 488 times because insufficient tissue was removed at the first operation. Not a single instance of regrowth of tissue was mentioned as a cause for the second resection. One hundred and five patients had had troublesome incontinence, both temporary and permanent. Subsequently, prostatectomy was performed on 172 patients on whom resection previously had been done, and this figure would probably be considerably higher if all patients on whom resections were performed could be accurately traced.

In almost every instance the men performing the largest number of resections were having the best results and recommended the operation for practically all types of prostatic obstruction. The majority recommended that the procedure be used only in carefully selected cases and limited it to the smaller atrophic glands and median bars and for use as a palliative measure in cases of malignant growth.

These results are convincing enough to show that transurethral prostatic resection is an operation of great usefulness and of tremendous value to the patient at the hands of a surgeon with sufficient experience and ability to make proper use of the instruments and equipment that have been placed at his disposal.

Thompson,[43] in a review of transurethral surgery at the Mayo clinic during 1935, emphasized the value of intravenous anesthesia by means of pentothal sodium,[44] which was used for 428 of 1,521 patients who were subjected to various transurethral procedures. This type of anesthesia was used especially for cystoscopic examinations which necessitated general anesthesia, manipulation of ureteral stones and removal of vesical tumors and for urethral dilations and other transurethral manipulations which could be completed satisfactorily within approximately thirty minutes. This anesthesia was also employed in a number of cases of prostatic resection when it was necessary to remove only a relatively small amount of tissue. The broad scope of the transurethral treatment of tumor of the bladder is considered. In 63 cases a tumor

43. Thompson, G. J.: Transurethral Surgery in 1935, Proc. Staff Meet., Mayo Clin. **11**:360-363 (June 3) 1936.

44. The chemical equivalent for pentothal sodium is sodium ethyl 1-methyl butyl thiobarbituric acid. This drug has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

of the bladder was removed with an operating cystoscope or was excised with the Stern-McCarthy electroresectoscope. Almost any pedunculated tumor can be removed completely at one sitting. A tumor which infiltrates the vesical musculature is, as a rule, not suitable for transurethral treatment and is approached suprapubically. Radon emanation seeds are frequently implanted transurethrally into a tumor of this type. Thirty-three patients were subjected to 39 attempts to remove calculi from a ureter. In 25 of these cases the stone was removed at the time of manipulation; the Councill stone extractor was used in most instances. The author stressed the necessity for great care in the use of this instrument. In 5 additional cases the calculus passed within a few days or a week after manipulation. In 3 cases manipulation failed; in 2 of these the calculus was removed by ureterolithotomy. Transurethral manipulation was therefore successful in more than 90 per cent of the cases. On 695 patients, transurethral prostatic resection was performed 765 times. Study revealed the average age of the patients to be greater than that of patients formerly subjected to suprapubic or perineal prostatectomy. Another point of interest was the fact that in only 7 of these cases was preliminary suprapubic cystostomy performed at the clinic. In 11 other cases this operation had been done previously elsewhere. Thus, only 2.6 per cent of the 695 patients were subjected to preliminary suprapubic drainage of the bladder. In 65 per cent of the cases there was no preliminary preparation involving the use of an inlying catheter, and in many of the remaining cases preoperative preparation lasted only a few days. The presence of pyuria in itself is not necessarily considered an indication for preoperative treatment. If renal function is poor, as evidenced by a value for blood urea of more than 150 mg. per hundred cubic centimeters, operation should be postponed, although several patients whose urea stabilized only slightly below this level and who excreted a large volume of urine daily were subjected to prostatic resection without fatality. The average postoperative stay in the hospital for the entire group was eight and three-tenths days.

Forty-two of the 695 patients had been subjected to prostatic resection in preceding years. In 15 of these cases a malignant tumor of the prostate gland was present, and therefore recurrence might be expected. In the other 27 there was benign hypertrophy. Of an original group of 2,347 patients subjected to transurethral resection, the percentage of reoperation to date, for both benign and malignant hypertrophy, is approximately 3.8. The simplicity and safety of transurethral resection urges repetition of the procedure on both patient and physician if the functional result is not entirely satisfactory, whereas this was not equally true when suprapubic prostatectomy was commonly employed. There was no death among any of the 1,521 patients subjected to transurethral

procedures except in the group of 695 patients who underwent transurethral prostatic resection. Of this group, 7 died, a mortality of approximately 1 per cent.

Rubritius [45] discussed the question of transurethral prostatic resection and surgical enucleation. He stated that the urologists should not be divided into two groups, namely, those performing resection and those performing prostatectomy. Every urologist must be capable of carrying out both methods.

Rubritius considered transurethral resection with reference to five groups of conditions.

1. In cases of stricture of the urethra the urethral tissues are usually infected. It is evident that when an internal urethrotomy is done in these cases, infection may enter the blood stream. One of Rubritius' patients died of abscess of the brain after internal urethrotomy. Since then he has not performed this operation. He expressed the belief that surgical resection of the urethra is the best method of treating short traumatic strictures that cannot be improved by the use of bougies. When the stricture is impermeable, he performs suprapubic drainage. Commonly a short time after drainage of the bladder, the stricture is permeable and can be dilated with sounds.

2. Rubritius stated that litholapaxy is a satisfactory operation but that it requires skill and practice. Many of the younger urologists have little skill and little practice on account of the rarity of vesical stones. Contraindications against litholapaxy are too large or too hard stones, stones in a vesical diverticulum or stones behind a large adenomatous prostate gland. If a vesical stone and obstruction of the neck of the bladder are present coincidentally, it is necessary to open the bladder and remove the obstruction and the stone at one time instead of performing resection together with litholapaxy. A surgeon not trained in litholapaxy has better results if he removes the stone by the suprapubic route.

3. European urologists are not enthusiastic about transurethral prostatic resection. Rubritius expressed the belief that when urethral and pelvic dilatation are present secondary to adenomatous hypertrophy, only prostatectomy can give complete cure. Transurethral resection, in his opinion, should be reserved for early cases in which there is a small amount of residual urine and in which the urinary disturbances are only mild, and also for cases in which renal function is reduced and the patient cannot endure the strain of a prostatectomy.

4. A papilloma of the bladder is best treated by transurethral methods. Only rarely is the tumor so large that it is necessary to open

45. Rubritius, H.: Die Grenzen transurethraler Operationstechnik, Ztschr. f. urol. Chir. u. Gynäk. **42**:21-30 (Feb.) 1936.

the bladder. Carcinoma is treated by partial resection of the bladder when possible, and if not, by suprapubic incision and coagulation of the growth.

5. The changes in the lower sections of the ureter also may be treated by transurethral methods. It is frequently possible, by cutting the ureteral orifice, to permit a stone in the ureter to pass into the bladder. Too much time must not be lost by conservative methods, thus missing the moment for the operation. Ureterocele may be treated by the transurethral method if it is small. If large, a suprapubic opening is required.

Chute [46] reported the case of 2 patients from whom he had removed good sized benign obstructing "regrown" prostate glands in the last few months; his father had successfully performed prostatectomy on these patients ten and eighteen years before, respectively.

The first patient was 59 years old when operated on in 1924. A one stage suprapubic prostatectomy was performed, and three small masses, largely intra-urethral, were enucleated in the usual manner without any difficulty. The microscopist reported that the hypertrophy was benign. Eleven years later the same patient again had acute retention, and a moderate sized benign prostate gland was removed.

The second patient was only 47 years old when operated on in 1916. A one stage prostatectomy was done, from which the patient made a satisfactory convalescence. After the operation the patient was well for almost fifteen years, but in the last three years he had had mild symptoms of recurrent prostatism, a few ounces of residual urine had begun to accumulate and rectal examination revealed a good-sized benign regrowth of the prostate. A two stage suprapubic prostatectomy was performed, the gland, which weighed 50 Gm., being enucleated in one piece.

Twinem [47] studied 40 cases of adenomatous hypertrophy of the prostate glands of patients 80 years of age or over. The chief facts in regard to 7 patients within the age group in this report who were treated prior to 1921 were as follows: Five patients were treated surgically, 2 by suprapubic cystotomy, 2 by suprapubic prostatectomy and 1 by a two stage perineal prostatectomy. Four of the patients died.

Thirty-three patients were treated since 1921. The average age in this group was 82.4 years; 8 of the patients were 85 or more. Symptoms of disorder of the prostate gland averaged forty-three months in duration. The longest period of duration was eleven years. Residual urine varied from 4 to 85 ounces (from 120 to 2,550 cc.); 12 patients

46. Chute, Richard: The Recurrence of Benign Obstructing Prostates Years After Prostatectomy, Tr. New England Branch Am. Urol. A., 1935, pt. 1, pp. 36-40; New England J. Med. **213**:55-57 (July 11) 1935.

47. Twinem, F. P.: The Very Aged Prostatic, J. Urol. **35**:349-352 (March) 1936.

had complete retention at the time of admission. The value for urea nitrogen varied from 9 to 55 mg. per hundred cubic centimeters of blood; the average was 25.13 mg. The average three hour excretion of phenolsulfonphthalein in functional tests of the kidneys was 39.4 per cent; the lowest excretion was 19 per cent, and the highest, 69 per cent. The time elapsing between admission and cystostomy varied from a few hours to twenty-one days; the average was approximately four days. Of those patients on whom a two stage prostatectomy was performed, the time elapsing between operations varied from eleven to thirty-four days and averaged twenty-two and three-tenths days. There were 10 deaths. Eight of the patients who died were classified as definitely poor risks, 1 as fair and 1 as good. The patient classed as a good risk was considered neurotic. Six of the 10 patients had definite evidence of cardiac pathologic lesions. One patient had bronchopneumonia on admission, 1 had uremic symptoms and 2 patients had marked chronic bronchitis. In elderly men, when factors are present indicating an unfavorable risk, it is considered advisable in some cases to send the patient home after he has recovered from the cystostomy and allow several months to elapse until he reaches the optimum condition for prostatectomy. If such a patient recovers satisfactorily from the cystostomy and increases in strength during his convalescence, the possibility for a satisfactory result after the second operation is markedly increased. The incidence of cardiovascular disease is high in this group of patients.

The total operative mortality in this series of cases since 1920 was 33.3 per cent. Of the 13 patients who underwent perineal prostatectomy, 3 died, a mortality of 23 per cent. The mortality in the group aged from 80 to 84 years was 24 per cent, whereas in those from 85 to 89 years it was 50 per cent. In a series of 1,049 prostatectomies reported by Young, 31 were performed on patients in this advanced age group, and 5 of these died, a mortality of 16.1 per cent. Three patients were more than 84 years of age, and all of these died. It is interesting to compare the high mortality among these aged patients who had hypertrophy of the prostate gland with the total mortality from prostatectomy regardless of age, which in highly rated urologic departments usually is from 4 to 8 per cent.

Carcinoma.—Hryntschak [48] discussed the problem of whether carcinomatous degeneration takes place in hyperplasia of the prostate gland or whether the tumor does not always grow out of the true prostatic

48. Hryntschak, T.: Die Behandlung des Prostatacarcinoms: Beitrag zur Pathogenese, Histologie und Statistik, Kong. internat. Gesellsch. f. Urol., 1936, pp. 74-81.

gland. This question has given rise to different opinions by different authors. Statistics about the frequency of carcinoma in the hyperplastic tissue differ greatly.

In this study the author has tried, by histologic examination of 310 specimens taken at operation, to approach the solution of the two most important problems, the pathogenesis and the histology of carcinoma of the prostate gland. Apart from the statistics derived from this work about the frequency of carcinoma, he has tried to discover such alterations as might account for the frequency of such a lesion in the prostatic hyperplastic tissue. Furthermore, he has tried to discover the first alterations in the tissue which might lead to carcinoma and to determine their value. For the sake of a better understanding, and on account of the great importance of the subject, as many photomicrographs as possible have been published with the report, as the consecutive alterations of the histologic aspects cannot be illustrated merely by words well enough to convey a uniform appreciation to other investigators.

When examining the microscopic sections, Hryntschak was soon struck by the appearance of foci of regeneration in a great number of cases of hyperplasia. Furthermore, he found out that these centers of regeneration were never lacking in any of the cases in which early carcinoma was present. This fact necessarily attracted attention. The suggestion that these centers of regeneration might stand in some pathogenic connection with development of carcinoma has proved to be fertile in results. Hryntschak expressed the belief that he has been able to prove, through deductions and photomicrographs, that it is possible to establish an uninterrupted chain of intermediate phases between regeneration and carcinoma, giving explanation of the pathogenesis of carcinoma of the prostate.

Regeneration in the true prostatic gland as well as in its hyperplastic parts certainly often develops from an inflammatory process, but it probably often develops also from trauma. Hryntschak's photomicrographs have shown that some of the groups of tubules must have gone through several regenerative processes, caused by constantly repeated lesions, and that all along these constantly repeated cycles of regeneration the morphologic aspect of these groups grow more and more irregular and atypical. Though these centers of regeneration have only been found in specimens taken at operation, it is known from the literature that analogous conditions exist in the true prostatic tissue.

The similarity between the histologic picture of carcinoma of the true prostate tissue and that of carcinoma of the hyperplastic parts of the gland can now be understood.

The centers of regeneration are never to be found in one spot alone but always on several spots of the prostatic hyperplasia, especially in

its peripheral zone. This corresponds to Hryntschak's experience that in most of the cases in which early carcinoma is present the lesion is in the periphery of the enucleated parts. This also explains his observation that in cases of early carcinoma the lesion seems to originate from more than one spot alone; the centers of malignant degeneration originate from different spots.

Another striking morphologic peculiarity of carcinoma of the prostate gland, emphasized by all authors, lies in the diversity of its forms. In the same case one may find in different parts the carcinomatous proliferation at one time as an adenocarcinoma and then again as a medullary, a scirrhous or a squamous cell carcinoma. Several authors have grouped these forms into several types. Hryntschak expressed the opinion, based on his researches, that carcinoma develops from multiple regeneration centers; he added that the malignant proliferations each issue from a separate regeneration focus and present diversities in their structure dependent on the different stages or kinds of regeneration. These individual carcinomatous foci then grow toward each other, penetrate each other and fuse, and in the end present the well known picture of carcinoma of the prostate gland. As he has not yet been able to give proof of this hypothesis, it can serve only as a hypothetic basis for further research.

His researches have proved that carcinomatous degeneration takes place also in the hyperplastic parts of the prostate. Statistics about the frequency of carcinoma in the hyperplastic parts versus its frequency in the true prostate gland reveal that carcinoma occurs almost twice as often in the latter as in the former. On this account, Hryntschak stated that he believes he has found the explanation in his conception of the pathogenesis of carcinoma of the prostate. The prostate gland is frequently and during a long time subjected to irritation leading to repeated regeneration; if carcinoma develops there more frequently than elsewhere, it may be accepted as an indication for the correctness of his suggestion, namely, that there is an etiologic connection between these two different proliferations of the tissues.

The problem of new development of carcinoma many years after prostatectomy may also be explained by these facts.

Blanc [49] reported that he had recently observed 2 new cases of an exceptional form of carcinoma of the prostate gland, a cystic type; this made a total of 4 cases that had come under his notice. These, together with only 3 similar cases that he had found recorded in the literature, were outlined.

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49. Blanc, Henry: La forme kystique du cancer de la prostate, J. d'urol. **41**: 13-27 (Jan.) 1936.

The condition is characterized by the presence of enormous cystic cavities, usually single, occupying one entire lobe of the prostate gland and filled with pure blood, blood serum or serohemorrhagic fluid, possibly mixed with débris from the lesion. The question arises whether or not such a cyst or tumor is primary. In 3 of the cases the view that the carcinoma was primary seemed justified; in the remainder it appeared that giant cysts had been formed by coalescence of multiple small cysts and that at some time during their evolution a neoplastic process had been superimposed. Why such cystic formations are so rare while epithelioma of the prostate is observed so frequently is not known. It is important to note, however, that this cystic process seems to develop solely on the prostate gland itself and not on an adenoma. The growths are primary glandular carcinomas and not adenomas that have become carcinomatous. It is possible that there may have been a simple coexistence of a prostatic epithelioma on the one hand and a prostatic cyst on the other, the latter being produced by neoplastic obliteration of certain glandular acini, without primary intramural hemorrhages but with secondary intracystic bleeding. The cyst would thus be added to the neoplastic process, which would remain clinically masked while continuing to evolve.

The symptoms at first are those of common prostatism, with rectal examination revealing nothing and with the clinical course differing in no respect from that of common epithelioma of the prostate. As time goes on, however, the peculiar aspect of the organ under rectal examination cannot fail to be noted. None of the common signs of epithelioma, namely, hardness, irregular deformity and lack of delimitation, are present. The prostate gland, greatly increased in size, bulges considerably into the rectum, but, contrary to what is observed in prostatic hypertrophy or in neoplasm, the two lobes are absolutely separated by a pronounced median furrow. This tumefaction, which is painless, has a clearly rounded form and a smooth, regular surface. Most striking of all is the elastic and fluctuating consistency, giving the impression of a collection of fluid. At no point of the tumor is there any hardness; the consistency is uniform and the wall so thin that the pressure of a finger-nail might tear it. In Blanc's patients this condition persisted unchanged for several months. In 2 of his cases and in the 1 case of Andre, the cystic masses reappeared after operation.

It is well to bear in mind the possibility of such a cystic form of carcinoma, since in most cases there will be nothing to suggest carcinoma of the prostate, either in the clinical history or on rectal examination. The diagnosis of a cystic tumor is evidently not difficult, and the presence of the characteristic median furrow eliminates the possibility of prostatic hypertrophy. The only difficulty will be in determining the benignity or malignancy of the cystic tumor, and this only

time can reveal. Blanc expressed the belief that one should always suspect the tumor to be malignant and be guarded in prognosis. It is difficult to state with precision the time required for evolution of cystic carcinoma of the prostate, since nothing is known of its beginning and too few cases are as yet on record.

Treatment can only be palliative. If rectal disturbances are severe, measures must necessarily be directed to the cystic formation itself, but if they are only slight, one may hesitate to operate on the cyst itself in view of the frequency of recurrence and the tendency of the tumor to continue its evolution. Measures that may be employed, if necessary, are rectal puncture, rectal incision, transperineal puncture, perineal incision after perineotomy and transvesical drainage. Incision by the perineal route appears to be the first and probably the best method to attempt. If diagnosis were certain, radiotherapy might be tried. Blanc stated that beyond attempts to keep up the patient's general health, the surgeon will have to be content with incision of the cysts by the perineal route and the performance of cystotomy when catheterization has become impossible or has to be done too frequently. He would not hesitate, however, in a new case to make an intraprostatic application of radium after perineal incision. Experience might show that deep radiotherapy is useful in these cases.

Oreja [50] stated that it is generally admitted that in 20 per cent of all cases prostatic obstruction is of carcinomatous origin; according to recent investigations, however, the proportion may be even higher. The fact that hypertrophy and carcinoma occur together causes the patient to perceive early the troubles peculiar to glandular hypertrophy, which induces him to consult a urologist at a stage of the disease when it may sometimes be admissible to consider the possibility of successful radical intervention.

With regard to the surgical treatment of cancer of the prostate gland, one of two main routes of approach may be chosen when one is proceeding to the radical extirpation of the carcinomatous prostate gland: the perineal or the suprapubic route. From discussions, it is obvious that the perineal route is used more often than the suprapubic route, which suggests that the results obtained by the former method are better. There is only one positive fact which may be recorded, namely, that the best results are obtained when the operation is performed only in cases in which cancer was thought to be present or in such cases in which a diagnosis of benign hypertrophy was made and the existence of the carcinomatous process is realized only in the course of the operation.

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50. Oreja, Benigno: Tratamiento del cáncer de la próstata, Kong. internat. Gesellsch. f. Urol., 1936, pp. 160-193.

Oreja concluded that in the presence of hypertrophy of the prostate gland in which small, suspicious nodules are perceived by rectal palpation, and with even more reason when the latter present themselves so vaguely that the diagnosis becomes still more doubtful, prostatectomy must be performed. On the other hand, in cases in which carcinoma is diagnosed with certainty, it is preferable not to operate.

Smith [51] stated that symptoms of carcinoma of the prostate gland do not manifest themselves until the neck of the bladder is involved. From 1919 to 1935 he has performed radical perineal prostatectomy after the method described by Young on 50 patients with this lesion of the gland. An analysis of these cases is submitted, and the technic of the operation with its indications and contraindications is considered.

In a large proportion of cases that part of the prostate gland which is palpable by rectum is the first to become malignant. In all but exceptional cases, carcinoma of the gland is of a stony consistency, with a tendency to form in the gland a ridge which has a relatively sharp edge, in contradistinction to the flat induration of inflammation or the symmetrically rounded surface of hypertrophy. In this series of 50 cases the diagnosis was sufficiently definite for the operation to be planned beforehand in 43 cases. In 7 cases the diagnosis was uncertain until the gland was exposed, when a specimen was removed for biopsy and frozen section was made immediately.

The technic of the operation may be briefly described as follows: The gland is exposed through a curved preanal incision. The urethra is opened at the apex of the prostate, and a Markley tractor is inserted. Denonvilliers' fascia is cut across and, by blunt dissection, is stripped off the posterior surface of the gland, thus removing the rectum from the field of operation. The lower half of the seminal vesicles are exposed. Laterally, the gland is practically free in the pelvis. The membranous urethra is cut across, leaving a cuff of urethra projecting from the triangular ligament. The apex of the gland is depressed and by blunt dissection with the handle of a scalpel is freed from the loose tissue anterior to it. This line of cleavage is followed until the anterior wall of the bladder, recognized by its circular fibers, is seen. This is incised, and the incision is carried down on each side of the prostate. The tractor is then removed, and the anterior commissure of the gland is seized with double hooks and drawn forward and downward; this exposes the trigon. The trigonal flap is then pushed upward off the vesicles, which are freed from in front and from behind. The attachments of their tips are clamped with rightangled hemostats and cut across. These clamps control the chief supply of blood of the prostate

51. Smith, G. G.: Total Perineal Prostatectomy for Carcinoma, J. Urol. **35:** 610-617 (June) 1936.

gland. The vasa deferentia are cut and tied just above their ampullae, and the vesicles and prostate gland are removed. The central point of the neck of the bladder anteriorly is then sutured to a corresponding point in the stump of the urethra. Two lateral sutures are placed on each side, and the tip of the catheter is inserted into the bladder. The posterior central point of the neck of the bladder is then sutured to a corresponding point in the urethral stump. Cigaret drains are placed to each vesicular bed, and the perineum is closed with catgut and dermal sutures except for the left lower angle of the incision through which the drains are led.

Constriction at the point of union of the urethra and the bladder developed in 6 cases. Dilation was required occasionally, but the condition seemed to be caused by scar tissue outside the urethra rather than by a true stricture. Even the patients who died of recurrence of the disease were unusually free from symptoms of obstruction. Only 2 such patients required suprapubic drainage. The degree of urinary control was excellent in 11 cases, good in 19, fair in 7 and poor in 6, while in 1 case the result was not given. A rectal fistula was present in 1 case. Of those patients with poor control, 1 was suffering from tabes and 1 was feebleminded. Five of the 50 patients in this series died in the hospital. Twenty-five others died of carcinoma, having lived an average of three years. Six lived more than five years, the longest period being nine and a half years. Three patients lived seven and a half years and were in good health for at least five years after operation. Of the patients who died from the disease, 11 had definite involvement of the vesicles that was noted at the time of operation. Fourteen patients were alive and well at the time of the report. Roentgenograms had not been taken, but all the patients were in good general health and were free from pain, and on rectal examination evidence of recurrence was not noted. The duration of life since the operation was as follows: 2 patients were alive seven years afterward; 2 patients, five years; 5 patients, from four to five years; 2 patients, from three to four years; 1 patient, two years, and 2 patients, less than a year.

TESTIS

Ectopic Testis.—Pace and Cabot [52] stated that a study of 24 retained testes in adults suggests that there is progressive deterioration as the years go by. Thus a specimen from a patient in the second decade revealed germinal epithelium which might have developed normally. The specimen from the other patient in this decade showed complete

52. Pace, J. M., and Cabot, Hugh: A Histological Study in Twenty-Four Cases of Retained Testes in the Adult, Surg., Gynec. & Obst. **63**:16-22 (July) 1936.

degeneration, and it is not improbable that the testis was undeveloped from the start. All of the 6 specimens from patients in the third decade revealed some degree of atrophy, but all had remaining epithelium which could have gone on to satisfactory development. Four of the 5 specimens from patients in the fourth decade revealed epithelium which might have developed normally. The fifth specimen was extensively atrophied. Two specimens from patients in the fifth decade had epithelium which might have developed, whereas 2 others had gone on to complete destruction. One of these was a testis retained within the abdomen, in which, on theoretical grounds, one would expect more complete atrophy. Both of the specimens from patients in the sixth decade revealed complete fibrosis and destruction. It did not seem reasonable to assume that these could reveal any important degree of regeneration. All of five specimens from patients in the seventh decade revealed extensive degeneration and hyalinization.

It is interesting and, the authors stated, important, to note that in the normal routine examination of these 24 specimens 3 were found which showed evidence of carcinoma. Two of these were from patients in the third decade who had a lesion described as adenocarcinoma. The third was from a patient in the seventh decade who had a lesion which was controversial.

These findings seemed to the authors to strengthen the opinion that the abnormally placed testis is much more likely to have carcinoma than the normally placed testis. It further suggests that rather more careful study of misplaced testes removed at operation or found at necropsy might shed still more light on this question, which is of great importance.

Campbell [53] stated that perineal testicular ectopy is an unusual observation. Eccles found 5 cases in 936 instances of undescended testis; Robertson recently reported a case in a boy aged 3 months, who was operated on. There are 99 cases recorded in the literature to date.

The perineal testis is subject to the same unfavorable factors as are organs in inguinal or other forms of maldescent. If the anomalous condition is permitted to persist, atrophy and loss of fertility of the gland are certain. The organ is subjected to ill borne trauma, and according to Dean the improperly descended testis is 200 times more likely to become the site of a malignant growth than is a normally descended gland.

Treatment is necessarily surgical. There is no preventive treatment. Unless the ectopic gland is producing symptoms, operation should be

53. Campbell, M. F.: Perineal Testicle, J. A. M. A. **106**:2232-2234 (June 7) 1936.

withheld until after the patient's third birthday. It is advisable, however, to transplant the testis to its normal scrotal position soon thereafter. Through an incision from 3 to 4 cm. long, the external inguinal ring and the upper portion of the ectopic spermatic cord are exposed. The incision begins just above the level of the external ring and extends downward in the scrotofemoral fold toward the ectopic gland. Between the superficial and the deep perineal fascial layers the testis will often be found firmly anchored by its gubernaculum. The gubernaculum is divided, so that a generous segment remains for suture to the depth of the new scrotal pocket. The cord, which will be found of ample length, is mobilized to the external inguinal ring and is examined for a hernial sac. The tunica vaginalis is now everted behind the testis. An adequate pocket is made in the scrotum to receive the testis. The pocket is turned inside out, and to its depths the gubernaculum is stitched with fine chromic catgut. Care must be observed that in transplanting the testis to the scrotum the cord is free from torsion. When the testis is properly placed, it is well to close the fascial ring of the upper part of the scrotum with two or three fine chromic catgut sutures to keep the testis down in the scrotum.

Orchitis.—Ohlmacher [54] stated that orchitis may appear in from two to sixteen days after parotitis and most commonly in from four to eight days. The fever tends to persist for from two to six days and falls by lysis. A rather imposing proportion of atrophy, as high as 60 per cent according to Catrin, is said to occur in the absence of operation, which, briefly, has in the reported cases consisted of making incisions in the tunica albuginea.

Involvement of the ovaries is uncommon. Involvement of either the male or the female gonad is definitely inclined to appear as a late complication. According to Osler, "the orchitis may occur before the parotitis, or in rare instances may be the only manifestation of the infection (orchitis parotidea)." He stated succinctly that "involvement of the ovaries is rare."

Ohlmacher reported a case of unusual orchitis parotidea without parotitis along with an exceptional case of primary oophoritis caused by the virus of mumps.

Tumor.—Smith, Dresser and Mintz [55] reported 100 cases of tumor of the testis assembled from a number of hospitals around Boston.

Teratomas occurred most frequently in patients between the ages of 20 and 30 years; embryonal carcinoma, in those between 30 and 40

54. Ohlmacher, A. P.: Orchitis and Oophoritis Parotidea (Osler): Report of Two Cases, J. A. M. A. **106**:2053-2054 (June 13) 1936.

55. Smith, G. G.; Dresser, Richard, and Mintz, E. R.: Radiation Treatment of Tumors of the Testicle, Tr. Western Branch Soc. Am. Urol. A. **4**:48-55, 1935; J. Urol. **34**:462-469 (Nov.) 1935.

years. There was no marked difference in these two groups in the rate of progress of the disease. A definite history of trauma was obtained in 13 per cent of cases; in 5 per cent, the uninvolved testis was or had been incompletely descended. In 3 cases the tumor was bilateral. In 15 per cent of the cases the patients apparently were well two or more years after orchidectomy. Six of these had not been subjected to irradiation. In only one patient in this group was metastasis detected. So far as is known, all patients who had metastasis when irradiation was instituted have died of the disease or still have metastasis. In only 40 per cent of the cases in this series was irradiation adequate. A standard should be established for roentgen therapy after orchidectomy. It is essential to irradiate the entire abdomen, as the most common site for metastasis is in the lumbar chain of lymph nodes. If the thorax is not included in the first series of treatments, diagnostic roentgenograms should be taken every two months for at least two years.

Hinman and Benteen [56] stated that attempts to ascertain the relationship of cryptorchidism to tumor of the testis have heretofore been based on statistical surveys and that it is difficult to find a more satisfactory method of study for this particular problem. The simultaneous occurrence of cryptorchidism and tumor of the testis has been reported frequently in the past. In different series this association has been noted at 12.2 per cent by Hinman, 15 per cent by Scott, 11.7 per cent by Chevassu, 13.5 per cent by Dean and 11 per cent by Rubaschow. Of 57 consecutive, histologically verified cases of tumor of the testis in the London Hospital, 15.9 per cent occurred in cases in which there was inguinal maldescent of the testis. In Hinman and Benteen's series of 40 cases of primary tumor of the testis, the clinical diagnosis in 39 was verified histologically. From 1913 to June 1, 1935, 39,359 male patients were discharged from the University of California Hospital. During this period a study was made of 155 patients with undescended testes. One of every 253 male patients had an undescended testis. The incidence of primary tumor of the testis was 1 in every 983 patients. Of the 40 primary tumors, 19 were classified as teratoma, 14 as seminoma, 6 as embryonal carcinoma and 1 as an embryoma. Trauma to the scrotum was noted definitely 11 times and questionably twice.

Primary neoplasms of the testis occur more frequently if cryptorchidism is present than if it is not. Whether all undescended testes are potentially malignant is a debatable question. Study of Hinman and Benteen's series showed that in 2 per cent of the patients who had undescended testis a tumor of that organ developed. The incidence of primary neoplasms of the male sex gland in the group in which

56. Hinman, Frank, and Benteen, F. H.: The Relationship of Cryptorchidism to Tumor of the Testis, J. Urol. **35**:378-381 (March) 1936.

the testes were descended was 0.09 per cent. The incidence of tumors arising in cases of cryptorchidism is reported as being from 11 to 15 per cent in different series. The group of Hinman and Benteen showed a correlation of 7.5 per cent. In other words, among approximately 40,000 male patients, seen at the University of California Hospital, tumor of the testis occurred 20 times as frequently in undescended testes as in those normally placed.

SPERMATIC CORD

Torsion.—Kinney [57] reported a case of torsion of the spermatic cord. About 250 cases of torsion have been reported in the literature. Many cases of atrophy of the testis are unquestionably caused by previous torsion. Early diagnosis is imperative, and detorsion can be successfully accomplished in the majority of cases only if the patient is seen within an hour or so after torsion has occurred. Even if detorsion can be performed, atrophy of the testis usually occurs. Torsion of the cord can occur at any age, but most frequently during adolescence. Etiology is of little assistance in the prevention, diagnosis and treatment of torsion. The right spermatic cord and testis as compared to the left are involved in a ratio of about 3:2. The treatment should be surgical, and an appeal is made for prophylactic surgical measures and for the inspection of the opposite side in all cases of torsion of the spermatic cord.

URETHRA

Stricture.—Riba [58] stated that for the division of urethral strictures he has developed a no. 12 French, semiflexible, insulated electro-urethrotome equipped with an expansible cutting loop. A standard filiform bougie is attached to act as a guide. After the urethrotome has been inserted, the loop may be expanded to the desired caliber just proximal to the deepest stricture. Contact is then made with a foot-switch, and the instrument is withdrawn. The current may be discontinued any time during the withdrawal. All cutting is done at a position corresponding to the figure 12 on the dial of a clock, along the surgical urethral roof and distal to the cut-off muscle. There is no shock and little active bleeding. Urethral anesthesia with a 1 per cent solution of cocaine has been used as a routine in all but 1 case. Patients who have urine in the bladder are able to void immediately after urethrotomy. An indwelling catheter is unnecessary.

A summary of cases of stricture in which electro-urethrotomy was performed is presented in the accompanying table.

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57. Kinney, W. H.: Torsion of the Spermatic Cord, Tr. Western Branch Soc. Am. Urol. A. **4**:32-38, 1935; J. Urol. **34**:470-476 (Nov.) 1935.

58. Riba, L. W.: Electro-Urethrotomy in the Treatment of Urethral Strictures, J. A. M. A. **106**:1971-1975 (June 6) 1936.

Urethritis.—Ormond [59] reported the results with the use of fever therapy in the treatment of gonorrheal urethritis of males at the Henry Ford Hospital. The air-conditioned Kettering hypertherm cabinet was used and was operated by immersing the nude patient, from the neck down, in air at a temperature of from 140 to 160 F. and at a humidity of from 35 to 40 per cent, so that the heat-regulating mechanism of the patient was rendered useless and his temperature increased. This method was used in 21 cases of gonorrheal urethritis which affected 20 patients in the past two years. The patients were divided into four groups. The first 4 patients treated comprised group 1. These patients received from two to four treatments at intervals of from four to eight days; the temperature was raised to 105 or 107 F. and maintained at that level for five hours. Posterior urethritis developed in 1 patient during treatment. A second patient refused treatment after the third dose. Two days later organisms were found in the urethral discharge, and three weeks later acute epididymitis developed. Three months sub-

Follow-Up Notes on Patients with Stricture who were Given Treatment

	Dilation (164 Cases)		Electro-Urethrotomy (49 Cases)	
	No.	%	No.	%
Returned	123	75.00	46	94
Failed to return	41	25.00	3	6
Improved	97	59.14	46	94
Unimproved	22	13.42	2	4
Made worse	2	1.22	0	0
Result unknown	2	1.22	1	2

sequent to this he did not present any evidence of gonococcic infection. A third patient refused further treatment when organisms were found after the second fever treatment and consulted another physician. The fourth man, a professional football player, received four treatments at weekly intervals; he played football between treatments. Four days after the fourth treatment gonococci were present in the discharge from the urethra. Group 2 consisted of 6 patients on whom the series of treatments was incomplete for various reasons. Group 3 consisted of 5 boys who were between 14 and 16 years of age. These boys were kept in bed, and fluids were forced moderately. They were given a bland diet, making the conditions favorable for obtaining the most satisfactory results. The first boy, who was seen three months after the onset of the urethritis, had only a small amount of discharge, which gave a specific reaction for the gonococcus. He was given one treatment at 107.2 F. for five hours; after this the urethral discharge disappeared. A month later there was no discharge, and the prostatic secretion did

59. Ormond, J. K.: Experience with Fever Therapy in the Treatment of Gonorrheal Urethritis, J. Urol. **35**:551-556 (May) 1936.

not contain any pus. The second boy, who was seen a month after onset of the disease, had gonorrheal urethritis and ophthalmitis. He received five treatments of five hours each, at intervals of eight days, at a temperature of 107 F. The ophthalmitis disappeared after the first treatment, and the discharge ceased after the fifth treatment. The third patient, who was observed two and a half weeks after the discharge appeared, received five treatments of five hours each, at weekly intervals, at a temperature of 107 F. Seven days after the last treatment gonococci were still present in the discharge from the urethra. Group 4 consisted of ambulatory patients.

In 2 of 15 patients who were ambulatory, complications arose during treatment, but they did not develop in any patient when he was undergoing treatment in the hospital. The treatment usually caused a prompt and striking decrease in the urethral discharge, and in the patients who completed the series the course seemed shorter than it usually is with the ordinary forms of treatment. The favorable effect of the treatment of complications was marked. Arthritis and epididymitis yielded promptly, and in the 1 case of ophthalmitis the condition cleared up after one treatment. While this is a small series of cases from which to draw conclusions, all who have used this form of therapy in these complications report the same results. Temperature as high as 107 F. has in most instances been tolerated well. An interval of three or four days between treatments is preferable, and the duration of a treatment should not exceed six hours. The disadvantages of this method of therapy are that it is somewhat of an ordeal, is expensive, necessitates loss of time from work and makes known the patient's disability. The majority of patients who have acute gonorrheal urethritis are young men with limited incomes who cannot afford to lose time from work. In the cases in which acute lesions were healed, the usual number of treatments was five, and there is no assurance that complications will not arise. The treatment is not free from danger, since death has occurred in the course of a treatment.

Sherman [60] reported on 400 cases of gonorrhea in males. Two hundred of these patients were treated by instillations of various antiseptic solutions, urinary sedatives, prostatic massage and the usual symptomatic treatment accepted by most physicians. The remaining 200 patients were treated by a combination of antivirus, vaccine and prostatic massage. All other treatment was omitted. The time required to stop the discharge from the urethra and to effect an apparent cure was shortened two and five weeks, respectively, by the use of antivirus solution. No deleterious effects were observed from the prolonged use of this solution. There was no increase in irritation of the urethra, no

60. Sherman, W. L.: Antivirus Treatment of Gonorrhea, J. Urol. **35**:546-550 (May) 1936.

burning and smarting on urination, no periurethral thickening and no stricture of the urethra in these cases. The occurrence of complications was 75 per cent less in the patients who were given antivirus than it was in those on whom ordinary treatment was employed. No cases of gonorrheal arthritis were observed. The administration of vaccine in small divided doses, given simultaneously at different sites, seemed to have a beneficial effect over the usual method of single injection.

VERUMONTANUM

Baldridge [61] reported a case of congenital hypertrophy of the verumontanum. The symptoms and pathologic changes in these cases are the same as those which are seen in cases of posterior urethral obstruction from any cause. Symptoms develop early or late, depending on the degree of obstruction and on the degree of compensatory hypertrophy of the musculature above the point of obstruction. Dilatation of the posterior urethra and bladder and extensive bilateral hydro-ureter and hydronephrosis are present. The ureteral valves are incompetent. Symptoms depend on the stage of the disease and on the presence or absence of infection. Those depending on the mechanics of the condition are difficulty in urination, dribbling, frequency and dysuria, but most important of all, intermittent distention in the lower part of the abdomen and paradoxical incontinence. The secondary group of symptoms, caused by renal failure, are those of uremia from any cause.

The author's patient was an 11 year old boy, whose chief complaints were hematuria and pain over the lower part of the abdomen and in both lumbar regions. Physical examination gave negative results except for the abdomen, which revealed extreme tenderness and muscle spasm in the region of the bladder and of both kidneys. There was an abdominal tumor in the midline, which extended from the symphysis pubis to above the umbilicus.

Two weeks after admission, during which time permanent drainage by means of a catheter had been instituted and the patient's urine had become clear of blood, cystoscopy was performed. The wall of the bladder was very thin and not trabeculated; it was generally congested. No diverticula, tumors or foreign bodies were seen. The verumontanum was enormously enlarged and filled the entire undilated portion of the posterior urethra. It protruded into the neck of the bladder and could be pushed from side to side. There were no demonstrable valves. The tumor did not bleed easily. It was destroyed as completely as possible by electrocoagulation, and permanent drainage by means of a catheter was employed.

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61. Baldridge, R. R.: A Case of Congenital Hypertrophy of the Verumontanum, Tr. New England Branch Am. Urol. A., 1935, p. 1, pp. 10-18; New England J. Med. **213**:46-49 (July 11) 1935.

On account of poor tonus of the bladder, the boy was unable to void after coagulation of the verumontanum, so suprapubic drainage was performed. After several weeks of suprapubic drainage, the sinus was allowed to heal and the patient was discharged, voiding normally.

UROGENITAL TUBERCULOSIS

Negley [62] stated that nephrectomy continues to be the procedure of choice in cases of positive unilateral renal tuberculosis and should be done as early as possible in order to avoid the complications of tuberculous cystitis or epididymitis. The high mortality in cases in which operation is not performed substantiates this dictum. The belief that any operation, cystoscopic manipulations or retrograde pyelograms are likely to induce terminal miliary tuberculosis or fatal toxemia is contrary to facts.

Spinal anesthesia, supplemented by solution of sodium amytal and sodium evipal [63] intravenously and the use of opiates, has been preferred by Negley for operations on both the renal tract and the genitalia. The significance of smears for acid-fact bacilli has not been sufficiently emphasized; a few negative smears are too frequently accepted as evidence that a patient is free from tuberculosis. Inoculation of guinea-pigs, as well as cystoscopy, should be carried out in every case in which urinalysis has disclosed the presence of albumin and pus after six negative smears. Every patient who has active tuberculosis should have acid-fast smears made at least once a month. Owing to the apathy of patients and also of the medical profession, the majority of cases of renal tuberculosis are not diagnosed until the late stages. In 400 necropsies on patients who had died from tuberculosis, there were no instances of healed renal tuberculosis. A tuberculin test of the skin has been done on inoculated guinea-pigs at the end of three weeks, and, although sufficient data are not available, it is believed that this will shorten the time required for diagnosis and add to the number of positive findings.

No patient who has tuberculosis of the genitalia should be dismissed without a complete study of the kidneys for possible renal tuberculosis, particularly those in whom urinalysis reveals tubercle bacilli. Vasectomy on the opposite side in tuberculous epididymitis or orchitis is always indicated, owing to the large percentage of cases in which involvement is bilateral (35 per cent). Orchidectomy is not indicated as often as is supposed. If care were exercised in the diagnosis and operative technic in epididymectomy, many testes would be saved.

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62. Negley, J. C.: Urogenital Tuberculosis, J. Urol. **35**:668-673 (June) 1936.

63. The chemical equivalent for sodium evipal is sodium n-methylcyclohexenylmethylmalonyl urea. Sodium evipal has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Of 139 cases of tuberculous epididymitis or orchitis, the prostate gland and vesicles were involved in 109 cases (84 per cent) and the kidney in 43 (33 per cent).

Lazarus and Rosenthal [64] stated that primary tuberculosis of the penis is a rare clinical entity, particularly when it occurs in adults, as only 25 cases (including the authors') have been reported to date. It is usually diagnosed late in its course, since it is most often mistaken for chancroid, chancre or granuloma venereum. The diagnosis can be confirmed only by histologic study and preferably by inoculation of animals.

The disease is characterized by a slowly spreading, painful ulcer with an indurated, bluish-gray border that has a marked tendency to become undermined and by a central ulceration covered with a dirty, yellowish, odorless slough. In the later stages, areas of cheesy necrosis may be seen near the indurated margin, and nodules are found in the region of the base of the ulcer. The lesion has a great tendency to scar formation, which at times breaks down to form new ulcers and is resistant to all types of treatment. Inguinal adenopathy is generally present but is never an outstanding feature of the disease. Urinary symptoms occur only when the urethra is involved.

In several cases the condition has yielded to excision or curettage of the lesion associated with the usual hygienic regimen reserved for generalized tuberculosis. Radical amputation is reserved for cases in which the glans penis and urethra are hopelessly involved. The prognosis is good in primary tuberculosis of the penis that occurs in adults. When the lesion occurs in children after circumcision, the prognosis is extremely poor.

A complete summary of the literature dealing with primary tuberculosis of the penis occurring in adults is given. An interesting case is presented of primary tuberculosis of the penis occurring in a young adult following sexual exposure, which necessitated radical amputation of the penis.

BILHARZIASIS

Diamantis and Xylinas [65] described their experimental production of bilharziasis in guinea-pigs, from which they obtained the following results: In 12 control animals (5 guinea-pigs and 7 mice), all males, that received injections under the skin of the abdomen of an emulsion of cercarias, the disease did not develop, not even in 1 that was allowed to live for three months after the injection. Of the 8 guinea-pigs which

64. Lazarus, J. A., and Rosenthal, A. A.: Primary Tuberculosis of the Penis, Tr. Western Branch Soc. Am. Urol. A. **4**:70-86, 1935; J. Urol. **35**:361-377 (March) 1936.

65. Diamantis, A., and Xylinas, E.: A propos de la reproduction expérimentale de la bilharziose chez les cobayes, J. d'urol. **41**:142-147 (Feb.) 1936.

served as subjects, the 2 that were infected by immersion of the penis in the emulsion died of cachexia, but neither of them presented the worms in any part of the portal system. In 1 of them, however, in which the liver was particularly affected, a small calculus, composed of calcium phosphate, was found in the bladder, as well as bilious and transparent urine. There can be no doubt that these animals died of hepatic insufficiency caused by intensive infection with the parasites. The questions arise why the parasites were not found in the portal vein and whether their death occurred before that of the animal. The authors were convinced that the parasites died first and that necropsy performed earlier would have revealed them in the liver.

Of the 6 other animals, which can be considered as having been infected by the classic procedure, none presented intestinal bilharziasis; that is, none had the worms coupled in the small ramifications of the mesenteric veins or eliminated them in their stools. Hence it must be recognized that among the 20 animals employed (13 guinea-pigs and 7 mice), some of which received injections of the emulsion while the others had the penis immersed in the emulsion, not even once was true intestinal bilharziasis found (with eggs eliminated in the stools), and only 2 infections were produced that were exclusively hepatic. The authors had the impression that they had delayed too long before killing some of the animals, for in the hepatic form, which is the one that as a rule develops in experimental bilharziasis in small animals, the parasites are far from being found at their ease in the hepatic trunk, that is to say, they are remote from any visceral mucosa, the submucous venules of which permitted them to copulate in the hepatic trunk, to lay eggs and to eliminate these. The authors concluded, therefore, that the hepatic trunk, far from being the favorite site chosen by the worms for their copulating and breeding, is simply a poor makeshift, a place where the worm, for lack of a better site, tries to get a foothold, not finding any venous recess short of the portal vein in which to ensconce itself.

UROGRAPHY

Minder [66] gave a detailed study on excretion pyelography, based on his experience in a Budapest urologic clinic. Retrograde and excretion pyelography are compared for different groups of diseases, and the value of both methods is illustrated by concrete cases. Minder stated that the problem of excretion pyelography does not lie in the technic of its application or in the indication for its use but in the judging of the pictures obtained. Such judgment may be obtained only after long experience.

66. Minder, Julius: Ueber den diagnostischen und klinischen Wert der Ausscheidungspyelographie, Ztschr. f. urol. Chir. u. Gynäk. **42**:312-363 (Aug.) 1936.

Braasch and Emmett [67] reported on a study of excretory urograms to determine their value as a test of renal function. The intensity of visualization of the medium in the urogram, together with its time of appearance, was used as a basis for comparison. In a series of 50 cases of various diseases of the urinary tract in which both excretory urography and differential tests with indigo carmine were used, the results obtained with the two methods were in close agreement in 39 cases (78 per cent). In 11 cases (22 per cent), the results of the two tests did not agree. Further study of a large series of excretory urograms was then made, the cases being grouped according to individual pathologic lesions of the urinary tract. The degree of visualization was compared with the results of other tests of renal function that had been done and with the pathologic changes observed at operation or necropsy. In hydronephrosis, pyelonephritis, polycystic disease and solitary cyst of the kidney the urograms seemed to indicate quite accurately the renal function present, provided certain rules as to their interpretation were followed. With regard to renal tuberculosis and calculous disease, the intensity of visualization in the urogram was often inaccurate in its estimation of renal function. Indigo carmine seemed to be a better index, but it also was inaccurate. However, the additional data furnished by the urogram as to the anatomic deformity present render it a valuable adjunct in the diagnosis of these conditions. In the field of malignant renal tumors, excretory urography will often suggest the amount of function remaining, but it is not reliable as an index to the extent of neoplastic involvement. With urinary obstruction such as is observed in hypertrophy of the prostate gland, excretory urography gives valuable information as to renal function. In this condition the picture of the anatomic deformity is exceedingly valuable, as dilatation of the upper part of the urinary tract is common and can be produced even in the presence of a normal urea content in the blood.

Emmett [68] warned against making a diagnosis of a completely functionless kidney on the basis of the excretory urogram alone. It is not uncommon, in the presence of stone in the ureter or renal pelvis, to fail to obtain visualization of the involved kidney, and yet on cystoscopic examination an almost normal concentration of indigo carmine may be excreted promptly by that kidney. Faulty technic in making the urogram may occasionally be the cause of failure of visualization. This in no way lessens the value of excretory urography, for in most cases the exact amount of function remaining to a kidney is not the paramount issue, and in those cases in which visualization is not obtained,

67. Braasch, W. F., and Emmett, J. L.: Excretory Urography as a Test of Renal Function, J. Urol. **35**:630-642 (June) 1936.

68. Emmett, J. L.: Pitfalls in Interpretation of Excretory Urograms, Proc. Staff Meet., Mayo Clin. **11**:411-413 (June 24) 1936.

other means are available to determine the viability of the kidney in question. The author presented the clinical record of a man 36 years of age, who complained of severe dysuria, with tenesmus, frequency of urination and hematuria. Cystoscopy was performed with the patient under general anesthesia. Both ureters were catheterized easily, and there was no evidence of obstruction. Both ureteral specimens revealed the presence of blood but no pus. Gram stains and stains for acid-fast bacilli were all negative. An excretory urogram made with both ureteral catheters in place revealed a normal renal pelvis, calices and ureter on the right side, but there was no visualization on the left side, even in the fifty minute roentgenogram. The ureteral catheters were left in place for about twelve hours and continued to drain hemorrhagic urine. Renal tuberculosis on the left side with a practically functionless kidney was suspected; however, a definite diagnosis was deferred. Conservative treatment was instituted, and one week later the symptoms were markedly improved. An excretory urogram made at this time revealed definite evidence of function of the left kidney. A retrograde pyelogram gave evidence of a normal renal pelvis, calices and ureter on the left side. Conservative treatment continued to result in improvement, and the symptoms were entirely relieved approximately five weeks after the institution of treatment. At this time an intravenous urogram revealed an entirely normal-appearing left kidney, pelvis and ureter. The exact diagnosis in this case remained somewhat in doubt, but the case serves to demonstrate the occasional evanescent nature of reduced ability of the kidney to excrete a urographic medium.

ANESTHESIA

Tovell and Thompson [69] stated that almost any type of instrumentation can be accomplished following the induction of anesthesia by means of the intravenous administration of pentothal sodium.[44] The 42 patients who were subjected to prostatic resection were for the most part those whose prostate glands were of moderate size and from whom it was necessary to resect 15 Gm. or less of tissue. Manipulation of a ureteral calculus can usually be completed easily within the duration of the anesthesia, as can also the various other minor operative procedures which have been previously mentioned.

Pentothal sodium is an anesthetic agent well suited in urologic practice for many cases in which a general anesthetic is required. It is best suited for adults when the examination or operative procedure is expected to be completed within thirty minutes. The safe maximal dose of the drug for intravenous administration is 15 grains (1 Gm.).

69. Tovell, R. M., and Thompson, G. J.: Pentothal Sodium Anesthesia in Urologic Practice, J. Urol. **36**:81-87 (July) 1936.

Coughing, gagging and other movements which interfere with the operator are seldom if ever encountered. Occasionally a patient will be encountered whose body will destroy the drug rapidly, or an operative procedure may be more time-consuming than expected. In these rather infrequent instances, following the injection of 15 grains of the drug supplementary inhalation anesthesia may be employed satisfactorily.

Pentothal sodium provides a safe and pleasant method of escape from those usually painful minor procedures which formerly necessitated the use of inhalation anesthesia or caudal or sacral block. Because of this fact, certain unpleasant sequelae of the latter methods can now be avoided.

Caporale [70] presented a method of anesthesia which is termed by Dogliotti as peridural segmentary anesthesia and which has been accurately studied in the Surgical School of Turin, Italy. This type of anesthesia has been used in more than 300 cases of renal and ureteral disease within the past four years, with excellent results. It is now used in approximately 95 per cent of the surgical cases of reno-ureteral disease at this school. The method consists of an injection into one of the last dorsal intervertebral spaces of about 30 cc. of a relatively more concentrated anesthetic solution than that in use for local anesthesia. This solution rapidly spreads around the dura mater, which easily separates itself from the vertebral canal; the solution spreads itself superiorly and inferiorly for a region of about from eight to ten vertebral segments. Thus it easily infiltrates itself in the intervertebral canals, along the spinal nerves, following the perineural lymphatics for a long distance out of the vertebral canal. The spinal nerves of the infiltrated region, because of the peridural anesthesia, are therefore surrounded by the solution which penetrates them and causes in about from fifteen to twenty minutes an intense and complete anesthesia of the respective region.

During the anesthesia there is no sign of dangerous hypotension or of interference with the fundamental functions of life. The anesthesia lasts about two hours, after which there is a slow return of sensibility. There is no postoperative nausea or vomiting, no postoperative cephalalgia, no signs of consequent disease on the part of the liver or kidneys or of metabolic changes. In the last series of 100 cases in which this anesthesia was used, successful results were obtained in an average of 92 per cent. In 6 cases it was necessary to use small quantities of ether or gas in order to terminate the operation. In 2 cases it was impossible to make an injection.

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70. Caporale, Luigi: Peridural Segmentary Anesthesia in Renal Surgery, J. Urol. **35**:403-407 (March) 1936.

URINARY ANTISEPTICS

Helmholz and Osterberg [71] mentioned that the work of Rosenheim in England has demonstrated that phenylglycolic (mandelic) acid, when administered orally, escapes metabolism or conjugation in the animal organism and is secreted in the urine in a concentration sufficient for bactericidal action, provided the p_H of the urine is lowered simultaneously. The authors studied experimentally and clinically the excretory rate of phenylglycolic acid following the oral ingestion by man and the intravenous injection into dogs of the sodium salt. Criteria were established for the concentration of the acid and the p_H of the urine necessary for bactericidal action on numerous strains of organisms which had been isolated from the urine of persons with infections of the urinary tract. Rosenheim's method was employed for studying the concentration of phenylglycolic acid in urine, and the quinhydrone-electrode technic was used in determining the p_H of the urine. It was demonstrated experimentally that sufficient phenylglycolic acid was excreted in the urine of the dog subjected to a continuous injection, during a period of seven hours, of 700 cc. of 1 per cent solution of sodium phenylglycolate to establish a bactericidal concentration of phenylglycolic acid provided the p_H of the urine was lowered to an optimal level for bactericidal activity. Such an injection gave evidence that any injury produced in the kidney by the injection of a solution of sodium phenylglycolate is only temporary. It was demonstrated that at a p_H of 5.0, a concentration of phenylglycolic acid of 0.25 per cent was bactericidal for most organisms. In a similar manner, at a p_H of 5.3 a concentration of 0.5 per cent, and at a p_H of 5.7 a concentration of 1 per cent phenylglycolic acid, was bactericidal. Just as in the case of beta-oxybutyric acid, so for phenylglycolic acid: The lower the p_H, the lower the concentration of acid necessary to secure bactericidal action. Clinical findings were reported in 1 case in which 3 Gm. of phenylglycolic acid, in the form of a 10 per cent solution of the sodium salt, was ingested four times during the day. Ammonium chloride was given, in addition, to lower the p_H of the urine. A concentration of phenylglycolic acid in the urine in excess of 1 per cent was obtained. Results of experimental work with various strains of organisms is reported in some detail. Certain members of the Aerobacter and Pseudomonas groups were found to be far more difficult to kill than the organisms of the colon bacillus group. The bactericidal effect of phenylglycolic acid on organisms of the coccic group has not been studied for a large series of organisms, but several strains of staphylococci have been tested in single experiments and have been found to correspond roughly in vulnerability to the organisms of the colon bacillus group.

71. Helmholz, H. F., and Osterberg, A. E.: The Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, Proc. Staff Meet., Mayo Clin. **11**:373-377 (June 10) 1936.